

ETHICAL PERSPECTIVES IN NEUROLOGY

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The practice of neurology presents a series of ethical challenges for the clinician. These rarely have simple or straightforward solutions, but require careful consideration by the neurologist. This section of *CONTINUUM*, written by colleagues with particular interest in bioethics, provides a case vignette that raises one or more ethical questions related to the subject area of this issue. The discussion that follows should help the reader understand and resolve the ethical dilemma.

NOTE: This is a hypothetical case.

A 27-year-old woman presents with a 3-month history of profound progressive visual loss in her right eye. She is admitted to the local university hospital, and work-up reveals that her visual loss is due to optic neuropathy from neurosarcoidosis. The attending physician has treated a number of patients with corticosteroid-refractory neurosarcoidosis with infliximab with great success. In this case, for the first time she would like to prescribe infliximab as a first-line agent to avoid the side effects of long-term corticosteroids. Infliximab is an intravenously administered chimeric (human and mouse) monoclonal antibody to tumor necrosis factor α (TNF- α) that is US Food and Drug Administration (USFDA) approved for the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis, Crohn disease, ulcerative colitis, psoriasis, psoriatic arthritis, and ankylosing spondylitis. Although usually well tolerated, patients receiving this medication are at risk of infusion reactions as well as rare but serious side effects such as drug-induced lupus, reactivation of tuberculosis, sepsis, pneumonia, CNS demyelinating events, and lymphoma. No USFDA-approved treatment of sarcoidosis exists, but corticosteroids are a mainstay of treatment. To date, published case series using infliximab in neurosarcoidosis have involved corticosteroid-refractory patients. The senior resident expresses concern about using infliximab first-line in an innovative off-label manner outside a clinical study approved by an institutional review board (IRB) when other first-line treatments have not yet been tried.

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COMMENT

- Physicians use medications “off label” when they prescribe a medication for a use that was not reviewed during the governmental regulatory approval process and is not included in the product information packaging (Gazarian et al, 2006). The USFDA is charged with regulating the production, labeling, and promotion of drugs. The USFDA, however, does not regulate “the practice of medicine.” Off-label prescribing is considered “the practice of medicine.” Therefore, the agency cannot proscribe physicians’ prescribing practices by limiting off-label drug use.

Undoubtedly, off-label prescribing is a widespread, often necessary, and an entirely legal practice. For example, many medications are never studied in children as part of the

USFDA-approval process, and thus a large proportion of medications that pediatricians prescribe for their patients can only be used off label. In fact, off-label usage may account for up to 90% of drug prescriptions in some in-patient pediatric populations (Gazarian et al, 2006). Neurologists, too, routinely use medications off label, such as tricyclic antidepressants, anticonvulsants, corticosteroids, azathioprine, mycophenolate mofetil, cyclophosphamide, and IV immunoglobulin, to treat disorders ranging from neuropathic pain and migraines to inflammatory disorders of the central and peripheral nervous systems. In fact, a retrospective review of one managed Medicaid plan revealed that 95% of patients on gabapentin were receiving it for an off-label indication (Mack, 2003). According to a recent survey of off-label prescribing practices of office-based physicians, approximately 150 million off-label out-patient prescriptions were written in 2001, 21% of overall use. In only approximately 30%, however, did strong scientific evidence substantiate the medication's use, raising important ethical concerns about the practice in these situations (Radley et al, 2006).

A certain subset of practice within off-label prescription—innovative off-label medication use—presents an even greater ethical challenge. Innovative off-label use involves prescribing that has a reasonable scientific or therapeutic rationale but lacks sufficient evidence of safety, efficacy, and cost-effectiveness (Ansani et al, 2006). In these situations, the stakes are often high because the patients are quite ill. However, the risks from the intervention are usually extrapolated either from other conditions for which the medication or procedure has been previously used or from an understanding of the way the diseased body should theoretically respond to the intervention. Further complicating matters is that in some instances the lines between the cutting edge of clinical practice and clinical research may appear blurred. This hypothetical case highlights some of the important ethical issues raised by innovative off-label usage:

- (1) How should the ethical principles of beneficence and nonmaleficence as well as patient autonomy and informed consent guide physicians engaging in the very common practice of off-label prescribing?
- (2) How have these principles influenced organized medicine's official statements on this practice?
- (3) How should physicians draw the line between the innovative use of new medical or surgical treatments and clinical research?

THE ETHICAL PRINCIPLES AND ORGANIZATIONS' RESPONSES

- Beneficence directs physicians to act for the benefit of their patients, and nonmaleficence guides physicians not to harm their patients as they strive to help them. Beneficence motivates the search for innovative therapies. Nonmaleficence cautions the medical community to examine the evidence for off-label prescribing closely and understand the scientific rationale for a therapeutic choice. Both principles, as well as an appeal to professional integrity, guide physicians to analyze outcomes carefully and share information with other health care providers so that others may either benefit or avoid harm from the therapeutic intervention. They also require physicians to prescribe medicines off label only when a favorable risk-benefit ratio exists. Finally, these principles may also call upon the physician to consider the financial toll that an off-label medicine may take on patients if third-party payers refuse to pay for unproven treatments.

Beneficence and nonmaleficence are only one dimension of the analysis. Without respect for patient autonomy, the physician, with all her good intentions, is free to impose unacceptably high risks on a patient without assessing a patient's desire to assume those risks. The principle of respect for persons and the principle of autonomy help control for these situations by imposing a requirement for informed consent for medical treatment and research subject participation. Before embarking on any therapeutic or research venture, a physician must obtain adequate informed consent from the patient. The risks and benefits associated with the intervention must be explained. Of course, the formality of the consent process may vary with the clinical situation. In a low-risk situation, the consent may be implicit, ie, the patient accepts prescriptions from a physician who has explained the indication for and common side effects of a medication. If this low-risk medication is being used off label, then an acknowledgment of its off-label status would be warranted for informed consent to be truly complete.

When a patient undergoes either a high-risk intervention or is a research subject, the informed consent process becomes very explicit and involves informed consent documents. Ideally, this process reintroduces an opportunity for a physician to communicate with the patient about the risks and benefits, rationale, and alternatives of the intervention, thereby preserving the patient's autonomy. When innovative off-label medications are prescribed, the medication's off-label status must be disclosed as part of the informed consent process and should be explicitly documented.

Informed by these ethical principles, a number of organizations have issued statements about prescribing off-label medications. In the United Kingdom, the General Medical Council (GMC) (2006) acknowledges the need for off-label usage, especially in children. The Council cautions physicians, however, to be satisfied that an approved alternative is not more appropriate, that there is a "sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy," and for the physician to take responsibility for monitoring outcomes and side effects. The American Academy of Pediatrics' (AAP's) Committee on Drugs (Agich, 2002) issued a position paper on the off-label use of medication, given the impact of this practice on pediatric patients. The AAP states that physicians must use "sound scientific judgment, expert medical judgment, or published literature" when using drugs off label. The USFDA (1998) similarly states that if "physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects." Thus, according to the official guidance of organizations that have spoken on the matter, the requirement of beneficence and nonmaleficence is met when the off-label usage is grounded in science and sound clinical judgment. Interestingly, the official statements are silent on the issue of disclosure to patients of the off-label status of the medications they are being prescribed.

In Australia, the New South Wales Therapeutic Advisory Group, an independent state government-funded organization, developed an algorithm to help clinicians assess the appropriateness of off-label medicine use (Gazarian et al, 2006). Like the guidelines from the GMC, AAP, and USFDA, the threshold question is whether "high-quality evidence" supports the use of the medication and there is "sufficient evidence about the medicine's safety profile to suggest an overall reasonable benefit-risk ratio for a given clinical context" (Gazarian et al, 2006). Furthermore, "the less serious the clinical need, the higher the level of evidence needed to support off-label use of the medicine"

(Gazarian et al, 2006). If high-quality evidence does exist, then the medicine may be used with disclosure of its off-label status. If no strong evidence exists, the medicine should not be used outside of a formal IRB-approved clinical research setting. Exceptions are made for truly serious conditions when standard therapy has failed and written informed consent is obtained.

IS INNOVATIVE OFF-LABEL PRESCRIBING RESEARCH?

- Generally, innovative off-label prescribing should not be conflated with research if the purpose of prescribing the medication is that it is part of routine clinical practice. According to the USFDA's "Guidance for Institutional Review Boards and Clinical Investigators" (1998), use of an approved medication, even off label, "when the intent is the 'practice of medicine' does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB). However, the institution at which the product will be used may, under its own authority, require IRB review or other institutional oversight."

The Belmont Report (1974), which articulated the ethical principles and guidelines for the protection of human subjects research, offers a more detailed understanding of the distinction between research and practice. According to the Belmont Report, "practice" refers to interventions designed solely to enhance a patient's well-being and have a reasonable expectation of success. Research, however, "designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge" (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1974). The Belmont Report's definition of clinical practice as requiring a reasonable chance of success offers an important nuance when considering off-label prescribing in general and innovative off-label prescribing in particular.

Furthermore, the Belmont Report cautions that "radically new procedures" should be subjected to the rigors of research "at an early stage in order to determine whether they are safe and effective." This language would prevent unproven therapeutic interventions from being undertaken routinely outside of IRB-approved research protocols in that a favorable risk-benefit ratio must exist for the intervention to be ethically sanctioned clinical practice. If that risk-benefit ratio is still unknown, we are in the realm of the experimental, and an IRB-approved research protocol would be the most appropriate way to answer the clinical question at hand.

Innovative therapy, however, often answers the call of clinical situations when there is no time for formal clinical trials. The more recently revised World Medical Association Declaration of Helsinki creates an ethical space for innovative treatments outside of research protocols by allowing the physician, with informed consent from the patient, to employ unproven therapies where other therapies do not exist or have been ineffective if in the physician's estimation such therapies offer hope of saving life, reestablishing health, or alleviating suffering. It then calls upon designing studies as soon as feasibly possible to study these innovations and at the very least to report the information in the medical literature (World Medical Association, 2000).

CONCLUSION

- ▶ In this case, the physician may justify using infliximab first line if there is adequate scientific or clinical evidence supporting its use in this patient with profound visual loss. The quality of the evidence to date comes from case series and case reports of patients who have done well on therapy when other immunosuppressive agents have failed, and so she may reasonably extrapolate that a treatment-naïve patient should respond favorably as well. There may be a reasonable argument about the timing of the onset of action of the various therapies and the risk this may present to the patient's vision. The physician must also discuss the risks and benefits of this treatment versus standard therapy and acknowledge the innovative off-label nature of this approach. She should also consider the financial impact of her therapy on her patient, especially if the cost will limit the patient's ability to follow through with the treatment. Finally, this one-time off-label usage need not be part of an IRB-approved clinical study since the purpose of using infliximab is for the benefit of the patient. Also, since this treatment has worked in patients resistant to other immunosuppressants, there is a high likelihood of success in this patient. However, the physician's local IRB or hospital Pharmacy and Therapeutics Committee is within its rights to review the innovative off-label utilization of this medication. The physician should consider studying this medication in the context of an IRB-approved study and should share her experience with the medical community through peer-reviewed publication.

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