4. Guidelines for the Allocation of Unproved Treatments

Background

All systems of health care have finite resources. No health care system can provide every item or service that might be desired by its patients or practitioners. Therefore, allocation decisions concerning how and where to spend the finite resources are inevitable in every health care system. Opportunity costs are incurred whenever allocation decisions are made. Opportunity costs refer to the fact that a decision to expend health care resources on one particular meritorious item or service implies the inability to expend those same health care resources on other competing potentially meritorious items or services.

Because of these opportunity costs, allocation decisions have ethical dimensions. The positive and negative impacts on patient health care resulting from expenditures on competing goods and services must be analyzed. Allocation decisions involving a choice between competing meritorious health care expenditures should include a utilitarian assessment of the resulting relative benefits and burdens to patients within the system.[1] Unproved treatments remain a controversial category of health care expenditures that incur opportunity costs. Experimental pharmaceuticals or other unproved therapies of alleged efficacy may be requested by patients or physicians outside of approved clinical-scientific trials. These unproved therapies often are expensive, scarce, potentially harmful, and of uncertain benefit. Indeed, because the outcomes of their use are unknown, ultimately they may cause

harm rather than benefit to the patient. Given their direct costs and opportunity costs, uncertain benefits, and potential for harm, what is the ethical duty of a health care system to provide unproven treatments?

Charge

The Subcommittee on Allocation of Unproved Treatments was charged by the VHA Bioethics Committee to study the ethical duty of VHA to provide unproved treatments to its patients and to formulate the principles governing the provision of unproved treatments.

Scope

This report concerns unproved therapies that may be requested by patients or their families, and occasionally may be requested by physicians, but for which no current mechanism exists for their provision. The class of unproved therapies forms a broad continuum of different treatments, all of which share the characteristic that their efficacy and safety have not been proved scientifically. On one end of the continuum stand those therapies anecdotally alleged to be beneficial, but for which no scientific evidence whatsoever exists for their efficacy or safety. On the other end of the continuum stand those therapies for which preliminary scientific evidence exists for efficacy and safety, but which have not been validated fully and therefore cannot yet be considered accepted medical therapies.

Many therapies on the anecdotal pole of the continuum have been labeled “alternative” or “folk” therapies because usually they arise from cultural or other popular, nonscientific sources. These alternative therapies may be requested by patients or their families as a consequence of their belief and hope that these therapies can be effective and safe when scientific therapies have failed, when scientific therapies are unavailable, or when scientific therapies are likely to produce undesirable side effects. Within some cultures, particular alternative therapies may have achieved an anecdotal popularity and desirability that is grossly disproportionate to the valid evidence of their safety or efficacy. A physician’s decision to consider providing

such alternative therapies requires a careful consideration of the relevant principles of clinical therapeutics as well as an understanding of the principles of justice.

Some therapies on the opposite pole of the spectrum have been called "emerging scientific" therapies. There is a continuum between emerging scientific therapies and accepted medical practices. Emerging scientific therapies gradually evolve from the laboratory to the clinic as evidence accumulates for their efficacy and safety. It is not intuitively obvious at which point along that continuum to draw the line separating an unproved emerging treatment from an accepted medical practice.[2] Therefore, adequate guidelines should acknowledge the reality of this continuum, apply equally well to multiple points along it, and not attempt to stipulate the point at which an unproved emerging scientific therapy becomes an accepted practice.

By intent, this report will not focus on therapies currently under active scientific investigation because existing programs and policies already provide guidance and mechanisms for the provision of such agents. For example, patients requesting this class of agents can be enrolled in approved clinical trials of the agent, can receive the agent through a "parallel track" mechanism if they cannot or choose not to participate in clinical trials, or can receive the agent from the manufacturer through a program of "compassionate use" outside of approved experimental protocols. When possible, patients requesting unproved therapies should be encouraged to enter clinical trials.

Standards

There are four fundamental principles or standards that form the backbone of the analysis of VHA's ethical duty to provide patients with unproved treatments. These standards are complementary. Each should be taken into consideration in a decision whether to provide unproved treatments. There is a hierarchy of importance of the standards. In descending order of their usual importance:

1. **The Standard of Efficacy**

   VHA's ethical duty to provide its patients with a particular unproved therapy for a particular disease increases as the evidence for efficacy of that therapy increases for the treatment of that disease.

2. **The Standard of Unreasonable Burden**

   VHA's ethical duty to provide its patients with a particular unproved therapy for a particular disease decreases as the burdens of that therapy increase for the treatment of that disease.

3. **The Standard of National Practice**

   VHA's ethical duty to provide patients with a particular unproved therapy increases as the evidence increases for its recommended use in accepted clinical practice guidelines drafted by expert panels.

4. **The Standard of Community Practice**

   VHA's ethical duty to provide its patients with a particular unproved therapy for a particular disease increases as that therapy becomes a community standard of practice for the treatment of that disease.

The Standard of Efficacy

There is a direct relationship between the evidence that an unproved therapy is effective and the ethical duty of VHA to provide it. With no evidence of efficacy, there is no ethical duty to provide it. With only preliminary, unconfirmed efficacy data, there is only a small duty to provide it. As more valid data are accumulated, the duty to provide it grows proportionately. Once there are adequate data to permit routine use of the therapy, the ethical duty to provide it becomes very great.

Efficacy outcomes for disease treatment can be measured either by the prolongation of life or by improvements in the quality of life. The efficacy standard can be applied accurately only when professionals with the clinical competency to properly provide the therapy are available.

The standard of efficacy should take into account the relative efficacies of alternative therapies available for the condition in question.

The Standard of Unreasonable Burden

There is an inverse relationship between the evidence that an unproved therapy is burdensome and the ethical duty of VHA to provide it.

Relevant burdens in this regard include the risks to the patient posed by the therapy and the direct and indirect costs of the therapy to VHA. The reasonableness of bearing the burdens will vary depending upon the severity of the illness in question.

As is true in all therapeutic decisions, the foreseeable risks of the unproved therapy must be balanced against its potential benefits in a utilitarian analysis. Only if the anticipated risks are justified by the expected benefits should the therapy be employed. Risks include all the expected or potential untoward consequences of the therapy, both physical and psychological. Risks also include the loss of benefits that may have resulted from the use of accepted and potentially effective therapies that were abandoned in favor of the unproved therapy. Additional risks to the patient may be produced if health care professionals lack the requisite clinical competence to correctly administer the proposed therapy.

The costs incurred by VHA include direct expenses, indirect expenses, and opportunity costs. The direct expenses refer to the monetary costs of providing the therapy. Indirect expenses include at least the costs of providing protection for legal liability for complications of the unproved therapy, and the costs of treating complications of the unproved therapy. Opportunity costs refer to the inability of VHA to use the money spent on unproved therapies for other meritorious goals.

The Standard of National Practice

As scientific therapies evolve in the transition from investigational to accepted practice, expert panels often publish clinical practice guidelines for their optimal utilization, based on the available scientific evidence for their efficacy and safety. The existence of relevant expert panel guidelines should be sought, and those guidelines that are available should be studied, because they provide evidence of nationally accepted standards of medical practice.

The duty of VHA to provide these transitional therapies increases in direct relation to the force of accepted clinical practice guidelines recommending their use. Headquarters can assist local VHA facilities in the identification of accepted clinical practice guidelines and also by providing a means for tracking the expenses and outcomes of these treatments.

The Standard of Community Practice

VHA has an ethical duty to provide its patients care, or access to care, the quality and comprehensiveness of which parallels that available elsewhere in the community. This duty increases in direct proportion to the extent that a particular unproved therapy becomes a community standard of care.

There are certain conditions for which a community standard does not exist because of the uniqueness of the condition in veterans or because of its general rarity. For example, the medical complaints of Gulf War veterans and those of Vietnam veterans exposed to Agent Orange probably cannot have a community parallel. In these instances, the community standard should be omitted and the remaining standards employed in the analysis.

Issues of Community Risk

There is a direct relationship between the risk to other unaffected patients in the community posed by a patient with a particular serious disease and the ethical duty of VHA to provide unproved therapies for

that disease, which would diminish that risk. Serious diseases that are contagious produce harms to other patients that may be diminished by reducing the disease spread and prevalence. The dimension of community risk implies a special duty to try to develop treatments for these diseases that reduce their prevalence and thereby decrease their spread to unaffected individuals.

Decision-making for VHA Facilities

Each VHA facility should be given the authority to decide locally whether to fund a given unproved therapy. This decision should be based on the benefits and burdens of the proposed therapy, and on the four standards for decision-making enumerated above. Any proposed unproved therapy should be subjected to rigorous scrutiny on these points and standards.

Each VHA facility should be permitted to choose who within the institution will be authorized to render such judgments. In many facilities, the Pharmacy and Therapeutics (P&T) Committee, or a subcommittee of the P&T Committee, will be best poised to make the decision. Not all unapproved therapies employ pharmaceuticals. The processes for analyzing the standards of efficacy, burden, national practice and community practice are similar for pharmaceutical and other therapies. The P&T Committee, or its subcommittee, in most cases has the greatest experience in conducting this method of analysis.

An appropriate method should be established within eachVHA facility to review and resolve disagreements between those who request unproved therapies and the decision-making body.

Social and Political Influences on Decision-making

Social and political factors may be raised by patients or families that may influence the decision to provide unproved therapies. For example, the dramatic changes in FDA regulations concerning the development and clinical use of new therapeutic agents for HIV/AIDS have been well documented.[3] In VHA, these factors may influence decisions to offer specific unproved treatments for various disorders,

e.g., HIV/AIDS, Gulf War illnesses, PTSD, or other conditions with political and social dimensions. However, these factors are not as relevant as the four standards and thus should not be given priority over them.

Recommendations

1. Each VHA facility should establish a mechanism for deciding whether and how to offer a requested unproved treatment. In many VHA facilities, the P&T Committee or one of its subcommittees will most efficiently fulfill this charge.
2. The agents responsible for rendering such a decision should carefully investigate the likely benefits and the burdens of the proposed therapy to the patient, the institution, and the system.
3. In rendering a decision, the agents should perform a utilitarian analysis employing the following standards, in order of their usual descending importance: the standard of efficacy, the standard of unreasonable burden, the standard of national practice, and the standard of community practice.

Notes

[1] These propositions are defended in Eddy DM. "Principles for Making Difficult Decisions in Difficult Times." *JAMA* 1994;271:1792-1798.

[2] An attempt has been made to provide criteria to separate standard and experimental therapies. See Reiser SJ. "Criteria for Standard versus Experimental Therapy." *Health Affairs* 1994;13(3):127-136.

[3] Freedman B. "Nonvalidated Therapies and HIV Disease." *Hast Cent Rep* 1989;19(3):14-20.

Appendix: Examples Employing the Guidelines

1. Hyperbaric Oxygen Treatment of Multiple Sclerosis

   A. Background

   Hyperbaric oxygen treatment using a therapeutic environment of O_2 gas at greater than atmospheric pressure has been used successfully to treat gangrene produced by anaerobic bacteria and decompression illnesses resulting from N_2 diffusion in deep sea divers. To provide hyperbaric oxygen treatment, a suitably equipped steel compression-decompression chamber and several skilled personnel are necessary. Currently, there are only about 15 such facilities in the United States.

   The idea that hyperbaric oxygen treatment might be beneficial for multiple sclerosis (MS) was based upon a theory of the pathogenesis of MS. As had been true in many other novel therapies alleged to be beneficial in MS, no controlled study of its alleged benefit was carried out when the anecdotal preliminary reports of its efficacy were published.[1] Nevertheless, following the publication of these preliminary reports, largely because this therapy sounded effective and safe and because there was no alternative offering better results, MS patients and their families began to contact physicians to request hyperbaric oxygen therapy. How should VHA respond to an MS patient or family member's request for this therapy?

   B. Analysis

      1. *The Standard of Efficacy*

      There are only uncontrolled reports alleging efficacy of hyperbaric oxygen in MS. Controlled studies are necessary to determine efficacy, particularly in a disorder such as MS with spontaneous remissions. In the subsequent controlled studies, no evidence of efficacy was found.[2] Therefore, VHA has no duty to provide this therapy on the basis of efficacy.

2. *The Standard of Unreasonable Burden*

   Hyperbaric oxygen treatment requires the availability of a hyperbaric oxygen chamber and a staff to run it. The chamber itself costs in excess of $2 million and annual staff costs probably add another $1 million. The treatment entails some risk of neurological dysfunction resulting from overexposure to oxygen at high pressures. The direct costs alone likely represent an unreasonable burden to VHA, in the absence of any strong evidence of efficacy. There are good data that other therapies, such as glucocorticoid therapy, interferon-beta-1b, and other immunosuppressive therapies offer a greater benefit. Therefore hyperbaric oxygen treatment fails this test.

3. *The Standard of National Practice*

   The data supporting the use of hyperbaric oxygen treatment for MS were reviewed by the International Federation of Multiple Sclerosis Societies Therapeutic Claims Committee. They found no convincing evidence of efficacy and therefore recommended against any MS patient undergoing this therapy.[3] Therefore the treatment fails this test.

4. *The Standard of Community Practice*

   Hyperbaric oxygen treatment for MS is not a standard treatment in any community. Indeed, it is not available in the overwhelming majority of American communities for the treatment of any disease. Therefore it fails this test.

C. Conclusion

VHA should not provide hyperbaric oxygen therapy for multiple sclerosis, even when requested by MS patients or their families, because of the lack of its efficacy, its unreasonable burden on the patient and the system, the recommendations of an expert international panel, and the availability of other, more effective therapies.

2. Use of Oral Interferon-alpha in the Treatment of AIDS

A. Background

Kemron, also known as the African AIDS drug, is a natural leukocyte-derived interferon-alpha (IFNα) substance. Interferons generally are not believed to be orally bioavailable. They are rapidly denatured (broken down) upon contact with gastric secretions. For clinical use, IFNα is formulated with powdered maltose into powder or tablet.[4] Patients are instructed to retain the compound in their mouths, sublingually, for up to five minutes to allow absorption by the oral mucosa prior to swallowing.

The initial study of low-dose oral interferon-alpha (IFNα), or Kemron, for the treatment of HIV infection was conducted by Koech and colleagues of the Kenyan Medical Research Institute. According to the study published in the Journal of Molecular Biotherapy in 1990, 8 of 40 (20%) HIV-infected patients treated for six weeks with low-dose oral IFNα showed a loss of seropositivity on ELISA and Western blot tests.[5] In addition to the sero-deconversion (or sero-reversion), the authors reported that patients showed a substantial rise in the CD4+ lymphocyte counts and improvement in clinical symptoms. Similar results were reported by Koech and colleagues in two subsequent reports. The studies were criticized for the lack of scientific rigor and lack of quality control for the CD4+ measurements.

The results reported by Koech and his colleagues led to the use of Kemron in some HIV-infected communities, particularly African American communities, and prompted further clinical research. In response to the widespread use of Kemron and other forms of low-dose oral IFNα by many HIV-infected patients and the controversy surrounding their use, the AIDS Research Advisory Committee (ARAC) of the National Institutes of Health requested that all information available on

this form of therapy be reviewed and a report be prepared for the committee by staff of the National Institute of Allergy and Infectious Diseases (NIAID).

In March, 1992, the ARAC examined the NIAID report containing summaries of 13 well-designed studies of low-dose oral IFNα. The beneficial results initially reported by Koech and colleagues were not reproduced by other researchers. Specifically, these studies were unable to duplicate the increases in CD4+ cells and conversion from HIV seropositivity to HIV seronegativity as initially reported by Koech and his colleagues. Based on this review, the ARAC recommended against the use of low-dose oral IFNα in AIDS patients.[6] Patients and their physicians were encouraged to carefully review the value of Kemron and other oral IFNs and to seek treatment with therapies whose efficacies had been established in well-designed, controlled clinical trials.

Despite the controversy and the scientific community's stance against Kemron and other oral IFNs, HIV-infected patients continue the use of these compounds. As a result, another large oral interferon-alpha trial was planned.[7] Dr. Lawrence Deyton, then Director of the Community Programs for Clinical Research on AIDS (CPCRA), had taken the lead in planning and funding this trial.[8] According to a commentary in *Treatment Issues*, because the issue of the efficacy of oral IFNα has been settled scientifically, this trial represented a waste of precious dollars and goodwill.[7]

B. Analysis

1. *The Standard of Efficacy*

Only one clinical study, that of the Kenyan Medical Research Institute, reported encouraging results from the use of Kemron. That study has been criticized on scientific grounds since it was uncontrolled and open-ended. There is no scientific evidence of the efficacy of Kemron.

2. *The Standard of Unreasonable Burden*

   The effects of Kemron are unclear. There was no indication of side-effects or physiological harm to patients. However, the cost of a drug that is not efficacious must be considered. Further, the psychological "cost" of a drug which patients incorrectly perceive as beneficial is not readily calculable.

3. *The Standard of National Practice*

   The ARAC reviewed data from a number of clinical trials and did not support the use of Kemron. Rather, the ARAC recommended that Kemron not be used in the treatment of HIV infection.

4. *The Standard of Community Practice*

   The use of Kemron is not a clinically accepted standard of community practice. However, some HIV communities, particularly African Americans, use and advocate for treatment with Kemron.

C. Conclusion

VHA should not provide Kemron for patients requesting the drug because it fails to meet the above standards. Other clinically effective therapies for HIV/AIDS should be provided for treatment.

Appendix Notes

[1] Neubauer RA. "Treatment of Multiple Sclerosis with Monoplace Hyperbaric Oxygenation." *J Fla Med Assoc* 1978;65:101; Neubauer RA. "Exposure of Multiple Sclerosis Patients to Hyperbaric Oxygen at 1.5 - 2 ATA: A Preliminary Report." *J Fla Med Assoc* 1978;67:498-504; Baixe JH. "Bilan de Onze Annees d'Activitie en Medicine Hyperbare." *Med Aer Spatiale Med Subaquatique Hyperbare* 1978;17:90-92.

[2] Sibley WA, ed. *Therapeutic Claims in Multiple Sclerosis*, 2nd ed. New York: Demos Publications, 1988:159-160.

[3] Fischer BH, Marks M, Reich T. "Hyperbaric Oxygen Treatment of Multiple Sclerosis: A Randomized, Placebo-Controlled, Double-Blind Study." *N Engl J Med* 1983;308:181-186; Bames MP, Bates D, Cartlidge NEF, et al. "Hyperbaric Oxygen and Multiple Sclerosis: Results of a Placebo-Controlled, Double-Blind Trial." *Lancet* 1987;1:297-300; Harpur GD, Suke R, Bass BH, et al. "Hyperbaric Oxygen Therapy in Chronic Stable Multiple Sclerosis: Double-Blind Study." *Neurology* 1986;36:988-991; Bames MP, Bates D, Cartlidge NEF, et al. "Hyperbaric Oxygen and Multiple Sclerosis: Final Results of a Placebo-Controlled, Double-Blind Trial." *J Neurol Neurosurg Psychiatry* 1987;50:1402-1406; and Kindwall EP, McQuillen MP, Khatari BO, et al. "Treatment of Multiple Sclerosis with Hyperbaric Oxygen: Results of a National Registry." *Arch Neurol* 1991;48:195-199.

[4] National Institutes of Health. *Interim Report: Low-dose Oral Interferon Alpha as a Therapy for Human Immunodeficiency Virus Infection (HIV-1): Completed and Ongoing Clinical Trials*. April 1992.

[5] Koech DK, Obel AO, Minowada J, et al. "Low-Dose Oral Alpha-Interferon Therapy for Patients Seropositive for Human Immunodeficiency Virus Type-1 (HIV-l)." *Molecular Biotherapy* 1990;2:91-95.

[6] News Release. National Institute of Allergy and Infectious Diseases, National Institutes of Health. Executive Summary - AIDS Research Advisory Committee. March 31, 1992.

[7] "Another Day, Another Trial: A Commentary." *Treatment Issues: Gay Men's Health Crisis* 1994;8(4):1-2.

[8] Deyton LR. Letter to CPCRA Steering Committee, October 5, 1993. Dr. Deyton became Director, VA AIDS Service, in January 1998.

Writers

Marvelu R. Peterson, Ph.D. - Chairperson
James Bernat, M.D.
Julia S. Hysom, M.A., M.H.A.
Jane F. Joyner, R.N., J.D.
Nancy M. Valentine, R.N., Ph.D., M.P.H., F.A.A.N.
Kathleen Zeiler, B.S.N., M.E