Problems and Benefits of an Antibiotic Compassionate Therapy Program

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So-called compassionate therapy can provide life-saving drug(s) for patients but can also introduce liabilities that may discourage such treatment. The procedures required for compassionate use of imipenem/cilastatin and a summary of the results of its use are used as examples. Physicians requesting drugs for compassionate therapy face problems in the timely acquisition of antibiotic from the manufacturer and the completion of the regulatory and patient case report forms. The pharmaceutical company encounters difficulties with the return of documents, the ability to use the treatment data for registration claims, and the assessment of outcome and safety in patients with multiple confounding medical problems. The benefits of compassionate therapy for all participants should favor its continued use. Suggestions for the improvement of compassionate therapy programs include streamlining of case report forms and more disciplined completion of forms by investigators.

Compassionate therapy describes the use of an investigational drug for a severely ill patient when no other effective treatment is available and when the requesting physician usually is not participating in a clinical trial of that drug. In many cases the illness is life threatening—for example, septic shock in a patient with neutropenia due to a multiply drug-resistant organism. In others it is less severe but markedly impairs daily activities—for example, chronic osteomyelitis due to a multiply drug-resistant organism. Although it might seem that such therapy would be of potential major benefit to those involved (patient, physician, and pharmaceutical company), significant liabilities are also associated with such therapy.

The rationale for requesting an antibiotic for compassionate use prior to regulatory approval relates to the antibiotic's activity against pathogens that are resistant to available antibiotics. Imipenem/cilastatin is a highly potent antibiotic active against organisms such as Enterobacter species, Acinetobacter species, and Pseudomonas aeruginosa [1]. Before the antibiotic was approved by the U.S. Food and Drug Administration (FDA) on 26 November 1985, Merck Sharp & Dohme Research Laboratories (MSDRL) granted >600 requests for its use in compassionate therapy in the United States. The problems and concerns raised during the compassionate therapy program for imipenem/cilastatin provide an understanding of the impact of such a program on patient, physician, and pharmaceutical company. To our knowledge such a review, which concentrates on the problems associated with compassionate therapy rather than on the outcome of the therapy, has not been presented before. We hope that it will lead both to a better understanding of compassionate therapy programs and to solutions to the problems they present.

Methods

Protocol. The protocol for entry of individual patients into this compassionate therapy program in the United States was similar to the protocol for a noncomparative study of imipenem/cilastatin [2]. It included background information, directions for obtaining cultures, dosage suggestions, clinical and laboratory safety instructions, and administrative and regulatory details. While proof of efficacy was not a primary concern in granting a request, FDA guidelines were given for assessing clinical and bacteriologic outcome. All adverse experiences or untoward events were to be reported and characterized as definitely not drug related, probably not drug related, possibly related, probably related, or definitely related.

Patient entry. No defined objectives or announcements of the compassionate therapy program were made to the medical community. Physicians requested the drug for compassionate use based upon their patient's need and information in the medical
Each request from a primary care physician was discussed with an MSDRL physician trained in internal medicine and infectious diseases. Entry required that (1) the patient have a life-threatening illness or a major infection impairing function (e.g., osteomyelitis); (2) the infection be caused by a bacterium that is resistant to all marketed antibiotics, or, in the case of \textit{P. aeruginosa}, susceptible only to an aminoglycoside; (3) the pathogen be susceptible to imipenem; and (4) the patient not have a history of hypersensitivity to $\beta$-lactam antibiotics. The dose of antibiotic was determined by the MSDRL physician based on severity of the infection and patient body weight and estimated creatinine clearance. The primary care physician obtained his or her department chairman's or institutional review board (IRB) chairman's approval for the treatment, and the patient signed a consent form before the antibiotic could be administered. (Subsequent IRB approval was requested.) The physician also agreed to complete all regulatory documents and case report forms and to report all adverse experiences to MSDRL. Infections involving \textit{P. aeruginosa} were treated with concomitant aminoglycoside whenever that organism was susceptible and the primary care physician wished to do so.

\textbf{Exclusion criteria.} In the early phase of compassionate therapy, patients requiring hemo- or peritoneal dialysis were excluded. Once limited information became available on imipenem/cilastatin pharmacokinetics in renal failure, that restriction was modified.

\textbf{Processing the request.} MSDRL sent a letter of instruction, the protocol, a consent form, and all regulatory documents by overnight mail to the primary care physician. A medical program coordinator at the pharmaceutical company obtained regulatory approval and submitted a request for the drug to the company's pharmaceutical development division. The antibiotic was packed and shipped to the requesting physician by express mail or chartered aircraft.

\textbf{Data collection.} The requesting physician was required to return all forms and unused drug to the company, with the assistance of an MSDRL medical research associate in the field if necessary. Additional information about adverse experience and patient progress was obtained by telephone.

\textbf{Results}

The majority of patients who received imipenem/cilastatin (hereafter referred to as study antibiotic) under a compassionate therapy protocol were treated after the U.S. New Drug Application (NDA) was filed in May 1984 (figure 1). Data from only 40 of 551 patients treated were available for inclusion in the NDA for the study antibiotic. The number of requests was at least 30% higher than the number of patients treated because of exclusion criteria and the decisions of physicians not to treat some patients even after the study antibiotic was sent. No eligible patient was refused treatment because of the unavailability of the study antibiotic even during the time of drug shortage in 1983.

For determination of the problems related to the type of patient treated, the conduct of the study and the quality of data collected, all 158 case report forms received by 31 December 1984 were reviewed. The characteristics of the 158 patients are listed in table 1. All patients had serious infections and significant underlying disorders. Their prolonged hospitalization prior to compassionate therapy was in large part due to their underlying illnesses as well as to the unsuccessful treatment of their primary infections with other antimicrobial agents. Respiratory infections were commonest. \textit{P. aeruginosa} was the commonest pathogen (88% of all cases). Background characteristics and the high percentage of \textit{P. aeruginosa} infections combined to give these patients a worse prognosis than patients treated in MSDRL clinical trials. If efficacy results were published for the compassionate therapy program, the pharmaceutical company would have difficulty comparing those
because patient background characteristics had a major negative influence. The clinical outcome could be determined for 155 of the 158 patients; no infection was diagnosed in the other three patients during the treatment period. The investigators listed 18% (28 of 158) cured, 50% (77 of 155) improved, and 32% (50 of 155) failed. Fourteen percent (22 of 158 patients) died during the course of therapy because of progression of infection, underlying illnesses, or a combination of the two. An additional 16 patients died in the 2-week period after therapy often because of causes other than the original infection. Therefore, 25% (38 of 158 patients) died within 2 weeks of therapy.

The use of concomitant drug therapy also had a negative influence on assessability, as indicated previously. According to FDA guidelines, patients are evaluable if treated with a single drug or treated concomitantly with an aminoglycoside to which the bacteria are resistant; thus, only 53 of the 158 patients (34%) were evaluable for efficacy based on clinical and bacteriologic outcomes. This group included all patients who failed on the combination of study antibiotic and an aminoglycoside to which the bacteria were sensitive. For some of the remaining 103 patients in whom pathogens were documented, the prior use of an aminoglycoside to which the pathogen was sensitive had not resulted in patient improvement. However, the aminoglycoside formed part of a successful regimen for these patients when used with the study antibiotic. Sixty-nine patients failed a treatment regimen that included the documentation of infection by criteria acceptable to regulatory agencies. In the imipenem/cilastatin study, all patients had pathogens that had been identified and tested for susceptibility before the antibiotic was requested. However, while other concurrent pathogens and body sites were often listed on the case report forms, the primary pathogens were omitted from the forms in a number of cases. Often the primary pathogen was not recultured prior to the initiation of therapy with the study antibiotic — only 141 of the 158 patients had one or more assessable pathogens at the start of therapy. In addition, 20 of the 141 patients had pathogens that could not be evaluated in terms of bacteriologic outcome. Therefore, bacteriologic outcome could be assessed in only 77% of the cases. No case without bacteriologic outcome could be used for submission to a regulatory agency.

Clinical outcome was easier to define than bacteriologic outcome, but patient background characteristics had a major negative influence. The clinical outcome could be determined for 155 of the 158 patients; no infection was diagnosed in the other three patients during the treatment period. The investigators listed 18% (28 of 158) cured, 50% (77 of 155) improved, and 32% (50 of 155) failed. Fourteen percent (22 of 158 patients) died during the course of therapy because of progression of infection, underlying illnesses, or a combination of the two. An additional 16 patients died in the 2-week period after therapy often because of causes other than the original infection. Therefore, 25% (38 of 158 patients) died within 2 weeks of therapy.

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Table 2. Adverse experiences for 158 patients treated under compassionate therapy with imipenem/cilastatin.

<table>
<thead>
<tr>
<th>Adverse experience</th>
<th>Probably or definitely drug related [no. of patients (%)]</th>
<th>All reported experiences without regard to drug relatedness [no. of patients (%)]</th>
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</thead>
<tbody>
<tr>
<td>Clinical only</td>
<td>13 (8)</td>
<td>66 (41)</td>
</tr>
<tr>
<td>Laboratory only</td>
<td>7 (4)</td>
<td>19 (12)</td>
</tr>
<tr>
<td>Both clinical and laboratory</td>
<td>8* (5)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Total</td>
<td>28 (18)</td>
<td>100 (63)</td>
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</table>

* Six clinical and two laboratory experiences.

same aminoglycoside used with the study antibiotic. When pretreatment sensitivity of the pathogen to the concomitant aminoglycoside was not used as an assessability criterion for these 69 cases, the overall assessability was 71% (112 of 158). The problem for the pharmaceutical company is that this larger number of cases would not be acceptable to the FDA under present guidelines.

The severity of illness and presence of multiple background illnesses may have had an effect on the number of reported adverse experiences. When all 158 patients were evaluated for clinical and/or laboratory adverse experiences regardless of drug relatedness (table 2), about two-thirds (63%) of all patients treated had some untoward event. However, clinical adverse experiences believed to be probably or definitely drug related occurred in only 19 (12%) of the patients, and laboratory adverse experiences in only 9 (6%). The spectrum of adverse experiences did not differ from those reported earlier [2].

The reported adverse experiences (especially death reported as an adverse experience) had a direct unfavorable impact on impending approval of the antibiotic. One foreign regulatory agency delayed approval of the study antibiotic until it received a report giving detailed opinions by the pharmaceutical company physicians and outside consultants that no deaths were related to toxic effects of the antibiotic. Even though the population characteristics had been given, the regulatory agency apparently had difficulty correlating the deaths with the severity of illness and the underlying risks.

Return of case report forms and regulatory documents was often delayed up to 7 months after NDA approval and therefore after compassionate therapy was essentially complete. Files were incomplete for 51% (283) of the 551 patients: 26% (142 of 551) were missing all documents; 25% (141 of 551) were missing one or more documents. Thirty-three percent (180) of the 551 case report forms were not returned even though some of those patients had been treated >1 year earlier. When telephone calls, telegrams, and visits failed to retrieve the needed information, certified letters were sent to those investigators with outstanding documents reminding them of their responsibility.

The costs of the compassionate therapy program were difficult to calculate because drugs produced in pilot plants cost far more than marketed drugs. For the 602 patients for whom the study antibiotic was shipped, the costs included the value of 25,600 g of study antibiotic produced in pilot plants, $52,000 for shipping the drug and documents, and 21 man-hours per patient for the preparation, shipment, and analysis of drug supplies, documents, case report forms, and regulatory reports.

Discussion

Although many books [4, 5] and articles [6, 7] have been written on the conduct of clinical research, few [8–10] discuss the treatment of patients on a compassionate or humanitarian basis. The articles and published abstracts in the latter group present brief reports limited to demographic analysis of the patients treated and the clinical outcome of compassionate therapy. Only Rodel [10] suggests, in his abstract on the compassionate use of the antihypertensive enalapril maleate, that such treatment offers both advantages and disadvantages in pharmaceutical research.

Many patients who might benefit from investigational therapy are excluded from clinical trials sponsored by pharmaceutical companies because of the severity of their condition or the unavailability of the compound [11] to their physician. In an effort to treat these patients, the physician might adopt portions of an ongoing clinical trial protocol for the treatment of the individual patient [12, 13]. Hanks [12] describes his concerns about these ad hoc treatment courses in oncology and notes, among other things, that the individual patient could be exposed to unwarranted risk of toxicity because the physician is acting outside the supervised trial. Such devi-
ations from the established program as change of dose or therapy schedule could “eliminate the program’s effectiveness.”

The compassionate therapy protocol provides a regulated vehicle for the treatment of patients outside regular protocols. The benefit of compassionate therapy is to an individual and not to a population. However, since the major method of testing new drugs is in large comparative trials followed by non-comparative trials in still larger populations, there is little impetus to review the results of compassionate therapy for individual patients. In fact, there could be a rationale for compassionate therapy programs for collecting only the data that are necessary for regulatory compliance. Thus, in “the competition between the ethics of individual benefit and the ethics of group benefit” [14], the analysis of the investigational drug in a large population is of more concern than the clinical outcome for an individual patient.

The benefits and problems related to compassionate therapy often depend upon the type of program involved. The program described in this report is a humanitarian program primarily for patients with life-threatening illness for whom no alternative suitable effective agent is available; drug approval is not the major goal of the program. More than 97% of the patients in the program were treated after the NDA was filed. The use of concomitant antibiotics prevented use of much of the data for new claims; overall the benefit to the company was outweighed by the benefit to the individual. Programs that are less restrictive in patient entry and that omit treatment with concomitant drugs may provide data that are more useful to companies filing claims for other unlicensed drugs [15].

Another type of compassionate therapy program involves the provision of an unlicensed drug for rare illnesses with little likelihood of achieving a specific claim (e.g., the use of ivermectin for onchocerciasis in the United States). Compassionate therapy has also been used for an approved drug such as Oraflex [16], which was withdrawn from general use but which was still useful for some patients when other anti-inflammatory medication was not. All examples of compassionate therapy reported in the literature have patient welfare as their primary objective. Some programs have a low likelihood of “secondary gain”; others may gain claims during an approval process or enhance the chance of approval.

The patient, physician, and pharmaceutical company all have major responsibilities before compassionate therapy can occur. The physician must decide if the investigational antibiotic is warranted and potentially beneficial, must inform his institutional review board of the proposed therapy, and must assume responsibility for submitting regulatory documents and case report forms. The patient (or the patient’s guardian) must agree to the treatment. The pharmaceutical company must judge the potential benefit-to-risk ratio for the patient.

Compassionate therapy may create many liabilities for patient and physician. To a patient on the verge of death or loss of limb the added risks may seem small, but side effects may adversely affect his or her condition [12]. The physician is usually unfamiliar with patient response or side effects of the new agent. His pharmacy and nursing staff are often unfamiliar with peculiarities of handling and delivery of unlicensed drugs.

The liabilities and benefits of a compassionate therapy program are summarized in table 3. For the pharmaceutical company, the liabilities include the cost of the program (staff time, drug and shipping costs), though relative to the overall clinical development program these costs are not very high. A

<table>
<thead>
<tr>
<th>Liabilities</th>
<th>Benefits</th>
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<tr>
<td>Cost to pharmaceutical company of processing, shipping, and providing drug free-of-charge</td>
<td>Greater availability of drug for patients</td>
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<tr>
<td>Possibility of creating drug shortage for programs leading to drug approval</td>
<td>Larger number of physicians gain experience with antibiotic</td>
</tr>
<tr>
<td>Little control by pharmaceutical company over conduct of study</td>
<td>Additional information on potentially difficult-to-obtain claims</td>
</tr>
<tr>
<td>a) Problems with efficacy evaluation</td>
<td></td>
</tr>
<tr>
<td>b) Delay in document return</td>
<td></td>
</tr>
<tr>
<td>Confounding variables in a severely ill population may affect usefulness of data</td>
<td>Possible enhancement of drug approval status</td>
</tr>
<tr>
<td>Higher frequency of adverse experiences in severely ill patients may skew safety database</td>
<td></td>
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</tbody>
</table>
The greater problem is drug availability, especially in the early phases of clinical trials when only limited amounts of the drug are available from pilot plants. The shortage of drug at one point in the imipenem/cilastatin trials was a major problem. At such times a decision has to be made whether to continue granting requests for compassionate use, thereby decreasing drug supplies for clinical trials and potentially delaying regulatory approval. Should the benefit to one be outweighed by the benefit to many?

The lack of direct supervision by the pharmaceutical company can lead to several problems. In clinical trials for drug approval, the company physicians can discuss the protocol requirements in detail with the physician-investigator. That opportunity is not usually available under the urgent circumstances of compassionate therapy. Although the positive-culture rate of 89% for initial cultures and the overall rate of 77% for initial and follow-up cultures were relatively good in this compassionate therapy program, they should have been better because all patients had identifiable pathogens with demonstrated susceptibility when the drug was shipped. The primary factor for the decrease in utilisable culture data was the lack of reculture just prior to administration of the study antibiotic. Delay in the return of data presents problems for the company. Yet physicians derive no benefit from completing regulatory documents when no further drug is needed, and pharmaceutical companies have no means of enforcing compliance.

Generalization of the results of compassionate therapy to other patient groups is invalidated by the presence of confounding variables in the data on these severely ill patients. In our study the decision was made to allow concomitant therapy for P. aeruginosa in patients for whom such treatment might be useful, thus reducing the applicability of study results to other patient groups. The 68% cure or improvement rate in this series is low compared to other noncompassionate treatment series [17] and presumably reflects the problems related to the patients’ severe infections and background illnesses. Because high risks and death rates have negative implications that cannot be satisfactorily evaluated in such uncontrolled studies, little detailed information is published on the results of compassionate therapy programs. Anderson and Mason [18] note that compassionate therapy “may at times be inefficient, costly, and negatively biased against the new agent.”

The patients in antibiotic compassionate therapy programs are more likely to have extensive medical problems than those in clinical trials and to suffer events that could be termed adverse experiences. The death rate of 25% and the clinical adverse experience rate of 51% are much higher than in general trials [17] but not unexpected given the severity of disease and background illness.

The major impact of the safety reporting from most compassionate therapy programs occurs after the NDA is submitted and before the drug is approved. In the compassionate antibiotic study (figure 1) most patients were treated during the FDA review period—May 1984 to November 1985. The adverse experiences from most of the compassionate trials were submitted during the review process and summarized in safety update reports prior to approval. Changes in safety profiles based on data from the compassionate therapy program might have resulted in altered labeling or delayed approval of the drug. The delay in registration of the study antibiotic by a foreign regulatory agency was a dramatic and costly example of the risk of compassionate therapy for the pharmaceutical company. In terms of enhancing a product image, the safest approach for the company would be to disallow compassionate therapy after the NDA is filed. However, this is the time when more people are aware of a drug’s potential utility.

Even in the face of multiple liabilities, patient, physician, and company should benefit from compassionate therapy (table 3). The patient should benefit most by receiving a potentially life-saving antibiotic not otherwise available. The physician can offer an additional treatment to the patient and can coordinate therapy with a pharmaceutical company physician. The pharmaceutical company can work with a larger number of physicians than those engaged in multicenter clinical trials. The company may gain an unforeseen efficacy claim. Finally the company may benefit by having regulatory agencies give the drug a higher priority for approval.

There are a number of ways to improve the present conduct of compassionate trials—studies of single patients with life- or limb-threatening illness due to a highly resistant microbe. In the approval process by government agencies, a specific category might be designated for these patients so that efficacy and safety are analyzed separately from those for general trials but would still be considered dur-
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ing package labeling. The requesting physician must understand both the importance of returning regulatory documents and data report forms and the regulatory criteria for documenting infections. Pharmaceutical companies may need to provide a smaller core package of forms in order to decrease the amount of physician time involved. Appropriate medical specialty journals might consider publishing criteria for admission of patients into compassionate therapy programs. Establishment of regional hospitals as depositories of drugs and disks for in vitro testing for compassionate use might decrease shipping costs in the United States and speed the delivery of drug to patient. Because of the problems associated with compassionate therapy, some drug companies might prefer to avoid such programs altogether. An understanding of the risks and benefits of compassionate therapy should enhance the interaction of patients, physicians, and pharmaceutical companies and help overcome a number of the problems.

References

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16. Oraflex may have compassionate use. FDC Reports 1984;46:12-3