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SPECIAL SECTION

On 6–8 April 1992 ALM International and GWL Hansen's Disease Center, Carville, held the ALM Consensus Development Conference on The Chemotherapy of Leprosy in Greenville, South Carolina, U.S.A. The Conference brought together clinical leprologists, pharmacologists, epidemiologists, leprosy control program managers, sociologists, health educators, and patient representatives to address the problems of leprosy chemotherapy and to develop recommendations to help clinicians involved in treating individual patients; program managers responsible for program planning, budgeting, and evaluating; and educators responsible for staff training and public education.

We are pleased to provide the published recommendations of this Conference.

Consensus Development Statement on the Chemotherapy of Leprosy

Introduction

The promulgation of limited-term multidrug therapy (MDT) for leprosy introduced by Professor Freerksen in 1972 (modified, further developed, and promoted on a worldwide scale by the Leprosy Division of the World Health Organization since 1982) has resulted in a significant decline in the known prevalence of clinically active leprosy cases in many countries. So much so that the elimination of leprosy as a public health problem by the year 2000 was accepted as a realistic goal by the World Health Assembly in May of 1991. In addition, newer regimens for the treatment of leprosy are currently under development which may very well reduce the duration of treatment necessary to effect a cure even further. Use of multidrug therapy in leprosy so far has been either in vertically organized leprosy programs or through relatively well-developed basic health services. Many practical problems will have to be faced in the use of chemotherapy to eliminate leprosy in areas where the prevalence of leprosy is low, populations are scattered, basic health services are meager, and referral hospitals are far distant from the patients' homes.

This conference brought together clinical leprologists, pharmacologists, epidemiologists, leprosy control program managers, sociologists, health educators, therapists and patient representatives in an effort to address these concerns and to develop recommendations which will help a) *clinicians involved in treating individual patients,* b) *program managers responsible for program planning, budgeting, and evaluating,* and c) *educators responsible for staff training and public education.*

Following two and a half days of presentations by experts and discussion by the audience, an independent consensus panel weighed the issues and prepared this statement in response to the following questions:

1. Are current WHO/MDT regimens* working satisfactorily in the field?
2. Based on results to date, can application of the WHO/MDT regimens be improved, particularly in relation to duration of therapy, the classification of cases, drug delivery, and/or the use of a single regimen for all cases?
3. Can the duration of chemotherapy be shortened significantly through the use of alternative regimens and what would be the practical impact of this on leprosy control, on patients and on program managers?
4. Are new strategies indicated for the delivery of chemotherapy and other aspects of

* Current WHO/MDT regimens:

For paucibacillary (PB) disease: Rifampin 600 mg monthly, supervised, plus dapsone 100 mg daily unsupervised both for 6 months. The 6 monthly courses of combined therapy must be completed within 9 months.

For multibacillary (MB) disease: Rifampin 600 mg with clofazimine 300 mg monthly, supervised, plus dapsone 100 mg and clofazimine 50 mg daily, unsupervised, for at least 2 years, and preferably to smear negativity. The minimum of 24 monthly courses of combined therapy must be completed within 36 months.

leprosy in the light of contemporary health, cultural, psychological, and economic factors?

5. What should be the focus of leprosy therapy research during the next decade?

CDC Statement

1. *Are current WHO/MDT regimens working satisfactorily in the field?*

As of February 1992, there were 3.1 million registered leprosy patients in the world including 600,000 newly diagnosed patients (1991). Forty-two percent or 1.3 million of the total registered cases were receiving MDT. Although these results are commendable, 58% of currently registered patients are not receiving MDT nor are the estimated 2.5 million undiagnosed patients.

Data from routine programs indicate that compliance is generally very good and WHO/MDT for multibacillary disease has a very high degree of efficacy, with total relapse rates well below 1% so far. Continued accumulation of data will be necessary to be certain that the relapse rate does not significantly increase in the interval from 5 to 10 or more years after completion of therapy, since the maximum period for which patient follow-up data is now available is only about 7 years.

Although therapy is often given to the point of negativity on skin smears, the recommended minimum of 24 months of MDT for multibacillary (MB) disease appears to be highly effective and longer therapy is not necessary even though the bacterial index (BI) on skin smears may not yet be zero. Studies indicate that the fall in BI will continue to zero even after therapy is completed.

The results with the 6 months WHO/MDT for paucibacillary (PB) disease are likewise excellent, with similar relapse rates. No change in the current regimen is recommended.

Classification of cases into PB or MB is sometimes a problem, as is the differentiation of relapse from reversal reaction. The clinical use of corticosteroids to differentiate relapse from reversal reaction has been proposed but has not yet been extensively evaluated under field conditions.

Acceptance of MDT including clofazimine has been very good, and serious toxicity from any of the drugs used is seldom reported. However, greater emphasis should be placed on recognizing and reporting side effects so that appropriate action can be taken if significant problems arise, for example, as a result of the HIV epidemic.

The coverage with MDT needs to be increased to reach the total population of patients in all countries as quickly as possible. This should be achievable in countries that already have a functioning basic health care system if they can accept the responsibility of MDT implementation, although MDT delivery systems may have to be simplified. Cultural, economic, and social issues such as the stigma often associated with the disease should be considered in planning implementation.

MDT has markedly decreased prevalence figures; on the other hand, in many countries little change in new cases reported (incidence) has thus far been noted. There is a long lag time between introduction of MDT and improved control and a fall in incidence. Where significant decline in incidence has been noted, it may on the other hand be due to improved socio-economic conditions, BCG vaccination and/or other factors rather than the introduction of MDT.

2. *Based on results to date, can application of the WHO/MDT regimens be improved, particularly in relation to the duration of therapy, classification of cases, drug delivery, and/or the use of a single regimen for all cases?*

At present, there is insufficient data to indicate that the standard WHO/MDT could be significantly shortened to less than the 6- and 24-month minimums recommended for PB and MB patients, respectively. Persisting viable *Mycobacterium leprae* have been found in about 10% of MB cases treated with currently available therapies. Although the significance of these persisters is uncertain, therapy that will eliminate or diminish them still further may be required to significantly shorten treatment. Thus far, HIV infection has not proven to be a risk factor for leprosy but continued awareness of this potential problem is advisable.

Classification into PB and MB disease remains important because it is not yet possible to recommend a single regimen given for the same duration for all patients. Cur-

rently classification is based on clinical findings and skin smears which are often unreliable. Other approaches include counting the number of lesions and the use of the lepromin skin test. Studies comparing these various approaches are needed to develop a simpler, more reliable, method of classification. Ultimately, a better system to differentiate PB and MB may await the development of serologic or other tests sensitive and specific enough to allow accurate classification.

Drug delivery is sometimes a problem, but MDT should be given even if every monthly dose of rifampin (and clofazimine for MB cases) cannot be supervised by a health worker. Use of persons outside the health care system should be considered in such cases to supervise therapy.

Although long-term follow-up is preferable, it should certainly no longer be a priority in areas where health care resources are limited provided the patient has understood that future problems may arise and has been advised to return promptly if symptoms of relapse, neuritis, reaction, etc., develop. Patients with such problems at the time of release from treatment require continued follow-up until the problem has been adequately treated. Those with deformities, lack of protective sensation or chronic eye problems will need care indefinitely.

The extent to which the so-called silent neuropathies develop for the first time or progress after completion of MDT is unknown. Studies to quantify the extent of this problem should be given a high priority since it may result in progression of an existing disability or new disabilities may appear. Trials to assess the role of the clofazimine component of MB-MDT in reaction and neuritis prevention are also indicated since new and more potent chemotherapeutic agents are being considered as replacements for this drug.

Although early detection and treatment of neuropathies and reactions is important for disability prevention it must be emphasized that to the extent possible early case detection followed immediately by MDT remains the best method to prevent disabilities.

When the goal of elimination of leprosy as a public health problem (prevalence less than or equal to 1/10,000) has been reached, resources will still be needed for case detection and treatment. New cases, and persons who have completed MDT but who are in danger of further disability, will also continue to need follow-up. Attaining a prevalence of 1/10,000 should be viewed as an indication that the program is successful but it will require continued funding to remain so.

3. *Can the duration of chemotherapy be shortened significantly through the use of alternative regimens and what would be the practical impact of this on leprosy control, on patients and on program managers?*

Recent studies have identified several new drugs (ofloxacin, sparfloxacin, clarithromycin, minocycline) with potent activity against *M. leprae*. These findings suggest it may be possible to further reduce the duration of chemotherapy in leprosy. However, there are insufficient data to justify endorsement of any particular new drug or regimen at this time.

In evaluating any new treatment regimen, the incidence rate of disabilities during and after chemotherapy is as important a measure of the value of a new regimen as the relapse rate. We, therefore, strongly recommend the use of the incidence rate of neuropathies/disabilities as one of the outcome measures in any drug trial, including the ofloxacin trial which is about to start.

The suitability of any new, very short chemotherapy regimen and its acceptability to patients are other important considerations. However, given the wide variety of field situations, no general recommendation concerning simplicity and acceptability can be made at this stage.

The toxicity of any new drugs and regimens should be carefully monitored. In general, only drugs suitable for oral administration should be considered for field use; the use of injectable drugs could lead to accidental HIV transmission. The use of new drugs outside a carefully planned drug development program and controlled trials is discouraged because it may lead to mere anecdotal evidence which in turn could result in widespread use of these drugs without adequate data on efficacy and toxicity.

The introduction of very short chemotherapy would have a major impact on control programs. It will certainly require the retraining of existing staff and reorganization of programs. Very short chemotherapy is likely to reduce contact with the patients and unless precautions are taken, disability prevention and the care of disabled patients might suffer.

In view of declining case loads (prevalence rates) vertical programs in many countries will have to consider either integration into the basic health services or a combination with another vertical program. The advantages and disadvantages of such moves must be considered very carefully. The ultimate goal is equal and adequate health care for all irrespective of the disease. Ideally, the standards of care for leprosy patients should not deteriorate in the process of integration or combination with another vertical program(s). The minimum requirements should be that MDT be maintained and that the treatment of reactions be continued. Whether or not basic health services can initially cope with the treatment of disabilities will inevitably vary from country to country, but such treatment should certainly be the goal.

Integrated programs should retain a specialized expertise for training and supervision and, at referral centers, for treatment of complications. Without such a component it will be impossible to maintain minimum standards of treatment and care in the long run.

4. *Are new strategies indicated for the delivery of chemotherapy and other aspects of leprosy in light of contemporary health, cultural, psychological, and economic factors?*

A better understanding is required of the economic, social and cultural factors which influence MDT coverage, case finding, compliance and other factors which may promote or impede leprosy programs. It is appreciated that elucidating cultural issues is not easy. Nevertheless, control programs should consider study of these factors as an essential part of their activities.

Substantial improvements are needed in communicating with patients and communities as well as in staff training and continuing education. These require strengthening at this stage, particularly if changes are to be made to chemotherapy regimens.

Early diagnosis and treatment under field conditions of nerve damage is an important aspect of chemotherapy. Thus the use of corticosteroids in the field is strongly recommended, but this should be accompanied by appropriate training of staff and careful monitoring for complications of steroid therapy.

For leprosy control purposes, a case of leprosy is defined as a patient who requires chemotherapy; however, other definitions are important which recognize the need for continuing care of patients who have completed MDT but are disabled.

The ideal chemotherapy regimen is one which is simple for staff and acceptable to patients. Further research is needed, but it is important that patients participate in the process of planning of leprosy programs at local levels and in the development of more acceptable chemotherapy regimens from the point of view of drug delivery, side effects, etc.

5. *What should be the focus of leprosy therapy research in the next decade?*

Our knowledge of the biochemistry and metabolism of *M. leprae* has markedly increased in the last few years. This has led to new *in vitro* methods of drug sensitivity testing, such as those involving the measurement of the metabolic activity of *M. leprae* by various highly sensitive methods. Some pathways unique to *M. leprae,* such as purine and pyrimidine scavenging activity and its synthesis of phenolic glycolipid-I, have been found which make attractive targets for the development of "designer drugs" to attack the bacillus. Unfortunately, new drug development is extremely costly. Thus, utilization of drugs developed for a different indication which also happen to act against *M. leprae* will probably continue to be the primary source of new chemotherapeutic agents for leprosy. Meanwhile, experimental and clinical studies should be supported to firmly establish the clinical value of drugs such as clarithromycin, minocycline and ofloxacin that are already under investigation.

Immunotherapy is an intriguing approach to the correction of the immune deficit that allows leprosy to develop. No preparation with great efficacy in this regard is yet available, and the development of a useful approach to this problem may await better understanding of the immune deficit involved.

Thus far the protective efficacy of BCG plus heat-killed *M. leprae* as immunoprophylaxis is not significantly better than BCG alone. Other vaccines are currently under trial. Vaccines developed using recombinant techniques are presently under study in the laboratory. Many trials with BCG have demonstrated significant protection against both MB and PB leprosy in many countries. Therefore, its continued application in leprosy-endemic areas is recommended.

A variety of new approaches potentially useful for the diagnosis and follow-up of leprosy have been developed in the last decade. These include the polymerase chain reaction and various tests to measure *M. leprae*-associated antigens or antibodies. These could provide a means for research on early diagnosis and follow-up of the disease. Unfortunately, none of the available tests have the sensitivity, specificity, simplicity and low cost required for use under field conditions. This work is important, however, and efforts should continue.

Standardized and appropriate statistical techniques (e.g., life table analysis) for assessing study outcomes should be used by all investigators.

Conclusions

1. Experience to date with the WHO/MDT regimen is very satisfactory. Toxicity appears to be minimal, patient acceptance is excellent and the relapse rate thus far is very low. Prevalence rates have fallen radically, but incidence rates have not yet shown a consistent fall attributable to MDT. The currently recommended durations of 6 and 24 months for PB and MB disease, respectively, appear to provide sufficient therapy. Follow-up is no longer required for uncomplicated cases where resources are limited provided the patients understand they must return at once if complications or signs of relapse develop.

2. A better understanding is required of the economic, social and cultural factors which influence MDT coverage, case findings, compliance, and other aspects which may promote or impede leprosy programs.

3. Application of MDT is not as widespread as desirable in many countries. Mobilization of additional resources and stimulation of political support are required to extend it to the whole population of leprosy patients in all countries.

4. Early diagnosis of leprosy and classification of the disease into paucibacillary and multibacillary types is sometimes difficult using currently available methods, but clinical findings and skin smears remain the basis for treatment decisions. However, the development of new serologic or other tests applicable in the field which would improve the early diagnosis of leprosy and follow-up of patients would be useful and should be further pursued.

5. Care and monitoring of patients' neuropathies and disabilities during and after treatment should be provided in any control program. The extent of disability development or progression after release from treatment needs to be accurately determined. Careful use of corticosteroids for treatment of neuropathies and reactions under field conditions should be encouraged.

6. New drugs may allow significant further shortening of therapy. The current trial of rifampin with ofloxacin should provide significant data in this regard. In evaluating any new treatment regimen, the incidence of disabilities during and after chemotherapy is as important a measure of the value of a new regimen as the relapse rate. Development of designer drugs specific for *M. leprae* is possible but may be prohibitively expensive.

7. Development of an antileprosy vaccine continues to be a priority. Methods utilizing recombinant technology hold some promise here. BCG offers considerable protection against the development of both multibacillary and paucibacillary disease. Until a more effective antileprosy vaccine is developed, use of BCG should be encouraged in endemic countries. Although effective immunotherapy would be useful, there is no data to support any of the current approaches to such treatment.

8. In view of the declining case loads, vertical leprosy control programs will have to consider integration into basic health services or a combination with another vertical program (e.g., tuberculosis or dermatology). The minimal requirements should be that MDT be maintained and that treatment of reactions be continued. In some countries basic health services may initially not be able to cope with the treatment of disabilities. An integrated program should maintain specialized leprosy expertise for training, supervision and management of complications.

Conference Postscript

An overview by the Chairman

The conference provided 3 exciting days of presentations and lively discussions among the attendees over the various issues covered. This document represents the consensus arrived at by the consensus panel regarding the 5 questions originally posed. The panel consisted of 10 members plus the chairperson, and considered input from the presentations, discussions and the relevant literature in preparation of this report. As such, I believe it accurately reflects the views of a majority of those participating. However, this does not mean that conflict and disagreement regarding some of these recommendations do not exist. During the opening session I quoted Senator J. William Fulbright, who, in a speech to the United States Senate in 1965 noted that, "Insofar as it represents a genuine reconciliation of differences, a consensus is a fine thing; insofar as it represents a concealment of differences it is a miscarriage of democratic procedure." Thus, it is appropriate to note the four points on which significant disagreements arose regarding the conclusions.

The recommendation that follow-up was no longer required after completion of therapy caused considerable debate. Concern was voiced that new or progressive disabilities would go undetected, detection of relapses would be delayed, etc. On the other hand, it was noted that follow-up after therapy was costly and difficult to maintain and patients could learn via health education to return at the first sign of any adverse event. Thus, the consensus that follow-up, while desirable, should no longer be a priority where health resources are limited.

Using disabilities as another measure of outcome of chemotherapeutic trials in addition to relapses also concerned some attendees. Strictly from a leprosy control point of view, disability measurement was seen as perhaps of lesser value, but many pointed out that from the patient's perspective it is even more important. At a minimum it should be determined that the disability rate is not significantly higher with any new regimen as compared with established ones.

The development of new methods for the early detection and classification of disease and follow-up of patients was seen by some as nonproductive and expensive, given the experience to date with serologic tests and the polymerase chain reaction. Others saw significant hope of success in this type of approach, however, and noted that major reductions in incidence and the goal of eventual elimination of leprosy as a public health problem may require such improvement in control techniques.

Lastly, giving vaccine development a priority status was felt by most participants to be important if true elimination of leprosy as a public health problem was to be fully successful since it is uncertain that improved chemotherapy and control efforts alone can accomplish this. Others argued that vaccine development and trials are extremely costly and use resources that might be better applied elsewhere, particularly since the chance of success may be small.

It is, thus, clear that strong differences of opinion did indeed exist on some of these issues. Nonetheless, in the end a consensus had to be developed based on the data available and taking into account the input and priorities of all panel members and participants. I believe that the consensus developed by the panel succeeded admirably in this regard, and the conference has thus made an important statement about the present status and future directions of leprosy control and research efforts.

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