Volume 72, Number 4
Printed in the U.S.A.
(ISSN 0148-916X)

INTERNATIONAL JOURNAL OF LEPROSY
and Other Mycobacterial Diseases

OFFICIAL ORGAN OF THE INTERNATIONAL LEPROSY ASSOCIATION

EDITORIAL OFFICE
Gillis W. Long Hansen's Disease Center
At Louisiana State University
Baton Rouge, Louisiana 70894, U.S.A.

VOLUME 72, NUMBER 4 DECEMBER 2004

EDITORIAL

Editorial opinions expressed are those of the writers.

The Relapse Rate in MB Leprosy Patients Treated with 2-Years of WHO-MDT is Not Low[1]

Robert H. Gelber, Ma. Victoria F. Balagon, and Roland V. Cellona[2]

ABSTRACT

A group of multibacillary patients is clearly at high risk for relapse following 2-yrWHO-MDT. Relapse is largely confined to BL or LL patients with a high BI initially, and occurs long after the discontinuation of therapy. This important group of patients at risk for treatment failure presents several important issues: the need to identify those at risk and the operational requirements needed for their long term follow-up. Also, this group of patients might well benefit from an alternative antimicrobial regimen from the outset, as well as upon relapse.

RÉSUMÉ

En conclusion, il y a clairement un groupe de patients multibacillaires présentant un fort risque de rechute après le traitement polychimiothérapeutique (PCT) de 2 ans qui est recommandé par l'Or ganisation Mondiale de la Santé (OMS). Ces rechutes sont lar gement restreintes aux patients lépromateux borderline et polaires avec un index bactérien élevé et se produisent bien après l'arrêt du traitement. Ce groupe important à fort risque d'échec thérapeutique soulève plusieurs questions sur le besoin d'identifier de façon prospective ces patients à risque, ainsi que sur les pré-requis opérationnels pour leur suivi à long terme. De plus, ce groupe de patients du début jusqu'à la rechute pourrait bien gagner à bénéficier d'un traitement antimicrobien différent du PCT de l'OMS.

RESUMEN

En conclusión, hay claramente un grupo de pacientes multibacilares que tienen un alto riesgo de recaída al completar la poli-quimioterapia (PQT) de 2 años recomendada por la

[1] Received and accepted for publication on 28 July 2004.
[2] R. H. Gelber, M.D.; M. V. F. Balagon; and R. V. Cellona, Leonard Wood Memorial Center for Leprosy Research, Cebu City, Philippines.
Reprint requests to: Robert H. Gelber, M.D., 220 Scenic Avenue, San Anselmo, California 94960. E-mail: ikgelber@hotmail.com

Organización Mundial de la Salud. La recaída está claramente confinada a los pacientes con lepra lepromatosa subpolar y lepromatosa polar, con un alto índice bacteriano, y ocurre mucho tiempo después de haber suspendido la terapia. Este importante grupo de pacientes en riesgo por falla en el tratamiento, requiere mayor atención. Se subraya la necesidad de identificar a lo pacientes en riesgo y la necesidad de implementar las medidas operacionales necesarias para su seguimiento a largo plazo. También se señala que este grupo de pacientes podría beneficiarse de un régimen antimicrobiano alternativo al terminar la PQT, antes de que ocurra la recaída.

The World Health Organization (WHO) recently declared that relapse after Multi-Drug Therapy (MDT) was "low" ([44]). This has not been our ([3]) experience with 2-yr MDT in multibacillary (MB) leprosy, nor that of two other groups ([17, 24]), especially in those with an initially high bacteriologic index (BI). We recently reported that in MB patients followed up by our physician staff for 12 or more years after the completion of 2-yr MDT ([3]), 13 (9%) of 142 relapsed both clinically and bacteriologically, and in those MB patients with an initial BI of ≥2.7, 13 of 98 patients (13%) relapsed. Since that study was completed, 4 more relapses in that cohort have been confirmed, resulting in a present relapse rate of 16% (17 relapses in 106 patients). Also, in patients treated with 2 yr WHO-MDT, the Marchoux Study Group (Mali) ([24]) reported after a mean follow-up of just 5 yrs that both clinical and bacteriological relapse occurred in 20% (7/35) of MB patients, and 39% (7/18) with a pre-treatment BI ≥4+. Furthermore, in Agra, India ([17]), after 2 yr WHO-MDT and a mean follow-up of 4 yrs, bacteriologic relapse was detected in 7% (20/260) of MB patients and in 17% (18/107) of those with a pre-treatment BI greater ≥4+.

There is certainly contradictory data demonstrating that relapse rates following 2-yr WHO-MDT for MB leprosy is low ([1, 5, 10, 27, 35, 36, 45]). However, these studies are wanting on several grounds, particularly, that data was either based on questionnaires, a short duration of follow-up, or a low percentage of patients with a high bacterial burden. A very recent study from Karigiri, India ([31]) in smear positive MB patients followed up for 16.4 ± 1.8 yrs also showed a low relapse rate (2 of 84; 2%) in MB patients, but that study admittedly had features that would prejudice towards that outcome: only 12% of those patients had an initial BI ≥3+; approximately half of the MB patients put on therapy could not be followed up; these patients had a significantly greater percentage of borderline lepromatous (BL) and LL patients, and a higher initial BI; many of these patients had received prior dapsone monotherapy, and more than half of the patients received more than 2 yrs of MDT, being treated until smear negativity. Nonetheless, in that study, 20% of patients with a BI ≥3+ relapsed.

Cebu relapse experience. In Cebu, our relapse definition required both new skin lesions and increased BI of 2+ in one or more smear sites than had been found on the last such evaluation. Our MB relapse experience after 2-yr WHO-MDT of 22 cases (some followed in the field) comprises the largest such group detected to date and the longest duration of follow-up in patients with an initially high BI. The experience reveals several clinical features.

Characteristics of lesions on relapses. Relapsed patients commonly present new lesions of the maculo-papular type and some localized infiltration on the body and extremities. Most localized infiltration, however, arose at old affected areas that had already subsided. A few plaques and nodules presented as new lesions. The lesions presented by the 22 relapsed patients are summarized in Table 1.

In all but 1 of our relapses, the BI had been 0 at 6 smear sites at the examination prior to relapse detection, indicating that these are indeed relapsed cases rather than treatment failures. The BI at the highest relapse site was generally high: 5+ (17), 4+ (3), 3+ (1) and 2+ (1). Also, very frequently, the earlobes were involved and infiltrated, with positive smears. Of the 22 relapsed patients, 12 (54.5%) had involvement of both earlobes with positive smears. An additional 5 patients (22.7%) had positive smears of 1 earlobe only. Involvement of 1 or both earlobes together were found in 17

TABLE 1. *The lesions presented by the 22 relapsed patients.*

a.	Macules, papules, localized infiltration	Found in 6 relapses
b.	Papules, localized infiltration	Found in 2 relapses
c.	Plagues only	Found in 1 relapse
d.	Macules, nodules	Found in 1 relapse
e.	Macules, papules	Found in 2 relapses
f.	Nodules, localized infiltration	Found in 2 relapses
g.	Localized infiltration	Found in 3 relapses
h.	Macules, localized infiltration	Found in 3 relapses
i.	Erythematous infiltration	Found in 2 relapses

of the 22 relapsed patients (77.3%). Thus, in addition to new skin lesions, more than three quarters of our relapses developed bacteriologic relapse in one or both earlobes.

Leprosy type and initial BI. All of the 22 relapsed patients were found to be clinically and histopathologically BL (10) or LL (12), in equal porportion to that found at the start of treatment. This implies that the risk of relapse is the same in BL and LL. No relapses were found in any of the borderline tuberculoid (BT) or borderline borderline (BB) patients followed up by physicians in this cohort.

Years elapsed after MDT when relapses occurred. The earliest of all relapses was detected 6 yrs after the completion of MDT. We found that the risk of relapse is nearly twice as much 10 yrs after treatment than prior to that time. This experience is summarized in Table 2.

Sex and age. The male to female ratio of the study population of MB patients was roughly 3:1. Of the 22 relapsed cases, 19 were males and 3 females, or a ratio of roughly 6:1. Though not statistically significant ($p = 0.13$), this suggests that males may have as much as two times the risk of relapse compared to females.

The age of the 22 relapsed patients ranged from 9 to 55 yrs at the start of treatment. We found a more or less equal proportion of relapses in patients initially treated in the young age group, 9 to 20 yrs old (8), middle age, 21 to 33 yrs old (7). This suggests that the risk of relapse is the same for leprosy patients independent of age.

BI after 2-Year WHO-MDT. Of the 22 relapses, 9 patients (roughly 41%) had already achieved negative smears after the 2-yr WHO-MDT treatment. This finding indicates that a negative smear after the end of treatment does not guarantee against future relapse.

However, all but one of the patients in the study eventually had negative smears in the 5 yrs after the end of treatment. In other words, almost all the relapsed patients passed through a period of negative smears before relapsing.

Effects of steroids on relapses. Of the 268 MB patients who were treated with the 2-yr WHO-MDT by the Cebu Skin Clinic (many with a follow-up of less than 12 yrs), 149 were given steroids because of lepra reactions, while 119 were not.

- Of the 149 given steroids, 9 relapsed (roughly 6.0%)
- Of the 119 with no steroids, 8 relapsed (roughly 6.7%)

The risk of relapse therefore appears to be the same for those given steroids during treatment and those that were not.

M. leprae sensitivity . The or ganisms taken from the biopsies of 16 clinically relapsed patients grew in the groups of mice not given any anti-leprosy drugs, confirming their viability and proof of relapse, while the results of 6 others are still pending. All of the or ganisms from the 16 patients did not grow in the groups of mice

TABLE 2. *Years elapsed after MDT when relapses occurred.*

Less than 5 years after the end of treatment	None relapsed
6 to 9 years after end of treatment	8 patients relapsed
10 years and above after treatment	14 patients relapsed

given rifampicin in their diets and clofazimine by gastric gavage. Two patients had organisms that grew in the groups of mice given the lowest concentration of dapsone (0.0001%) but not higher concentrations ("partially resistant"), and 1 patient harbored *M. leprae* that grew in mice fed 0.01% dapsone diet ("fully resistant.") These 2 patients are therefore mildly resistant to dapsone. It is noteworthy that Matsuoka has found no genetic mutation towards dapsone resistance in any of our 16 relapsed patients (personal communication). This discrepancy between that analysis and the results in the mouse footpad requires our further study. In any event, MDT does not appear to result in drug resistant relapse, nor , in particular , multidrug-resistant relapse.

IMPLICATIONS

Our relapse experience is particularly noteworthy in that all of our relapses occurred in BL or LL patients, and all but 1 relapse was found in patients with a pre-treatment BI ≥2.7 ([3]). In Mali ([24]) and in Agra, India ([17]), 25 of the 27 relapses (93%) occurred in patients with a pre-treatment BI ≥4+. In Karigiri, India ([31]) the two relapsed patients were among the 12% of those in that trial with an initial B.I. ≥3+, having a B.I. of 3.0 and 3.5. Thus, in all four studies a high initial BI was found to be a significant risk factor for subsequent relapse. Until the last decade, skin smears and the importance of precise clinical and pathologic classification across the leprosy spectrum were viewed as critical tools for choosing the appropriate regimen of treatment, as well as to predict response to therapy and subsequent reactional states. Today skin biopsy is practiced in a small minority of endemic locales, and an even smaller proportion of those where it is done are experienced with the interpretative skills required for placing a patient in the proper pathologic designation. Also, skill at skin smears has waned to the point that it has been found inaccurate in most locales, such that the WHO ([46]) no longer advocates its use in classifying patients as MB or PB. This distinction is now determined simply by counting the number of skin lesions, MB being 5 or more and PB being less. Such an approach is especially wanting and hard to support insofar as BL leprosy can often present with less than 5 skin lesions and at times but 1. Of utmost relevance to the lost use of skin biopsies and skin smears is that without them identification of those MB patients at high risk for relapse is lar gely unavailable worldwide.

Another observation from our relapse experience in the Philippines is that MB relapse occurs long after the discontinuation of 2-yr WHO-MDT. Of our 22 relapses, the first was detected 6 yrs after the discontinuation of therapy, and 14 were found 10 or more years after therapy ended. A similar experience was reported by Pattyn ([32]) after a 6 week intensive quadruple regimen (rifampin, ofloxacin, dapsone, and minocycline), wherein relapses were first detected at 6 yrs with a doubling in years 8 and 9. The Marchoux Study Group ([24]) found that MB relapse after 2-yr WHO-MDT occurred at a mean of 6 ± 1.5 yrs after the completion of therapy, while in Agra, India ([17]), where relapses were defined on bacteriologic grounds about 30% of the time without concommittant clinical manifestations, the average time to relapse was 4 yrs. Also in Agra, relapses were significantly higher in those MB patients followed up greater than 4 yrs than in those followed up for a lesser duration ([17]). Finally, in Karigiri, India, the two relapses detected were found 14 and 15 yrs after the completion of therapy ([31]). These experiences of late relapse following treatment for MB leprosy are in sharp contrast to the experience with short-course therapy for pulmonary tuberculosis, wherein 90 of relapses occur within the first year post-therapy . This has operationally led to the general policy of follow-up for patients with active pulmonary tuberculosis in the United States to be completed 1 yr after discontinuation of therapy. In any event, after the completion of WHO-MDT, there is currently no recommendation for follow-up at all and certainly not for the decade or longer needed to detect clinical and bacteriologic relapse ([46]). Perhaps the dramatically longer relapse interval in MB leprosy , as compared to pulmonary tuberculosis, is a reflection of the relative doubling time of the different mycobacteria, i.e., one day for *M. tuberculosis* and 14 days for *M. leprae.* Another possible factor is the higher bacterial load that may need to be attained in leprosy

prior to the development of signs and symptoms.

In many control programs today, once MDT is concluded for leprosy a patient is no longer considered a case and follow-up is not mandated. Thus, relapses in leprosy are largely left to self-referral and not to active and organized interventional follow-up by the health services. This, coupled with the long interval between the completion of MDT and the appearance of relapse, will likely result in a delay of relapse diagnosis and an increased rate of relapse morbidity. This potential is further heightened by our observations that relapse frequency in the Philippines was found to be lower (3%) when patient follow-up was conducted by even well-trained and experienced leprosy health workers rather than our physician staff ([3]). Worldwide relapse detection is further compounded when that diagnosis, is left to the general health services, which is now largely becoming the case. Fortunately, in our relapse cases, relapse was not associated with neurologic deterioration. Perhaps this salutary result was in part a function of prolonged, active, annual follow-up and by trained leprologists. Neither of these conditions are reasonable expectations in most endemic locales today, thereby again increasing thepotential risk of seriously delaying the diagnosis and the further possibility of increasing the risk of associated increasing peripheral neuropathy.

The relapse rate we and two other groups have noted is clearly high and would be considered unacceptably so in the treatment of pulmonary tuberculosis, where regimens which result in relapse rates greater than 5% have been rejected as unacceptable ([2]). Though there are no significant data on relapse following the current WHO recommended 1 yr ([46]) or 6 month MDT trials ([43]), there is little doubt that therapy for such short durations would result in relapse rates at least as high as 2-yr MDT. These regimens are therefore clearly difficult to support. Importantly, because the planned follow-up duration of the current WHO 6 month MDT ([43]) is only 5 yrs, a period shorter than our earliest relapse following 2-yr MDT, the follow-up in that study requires expansion to at least 15 yrs if meaningful data on relapse rates are to be obtained. Furthermore, we (unpublished) have found that both Type 1 and Type 2 lepra reactions, occur in a significantly larger percentage of patients, with greater frequency and for longer duration following 1-yr MDT as opposed to 2-yr MDT. This important additional morbidity and particularly its propensity for increased nerve function impairment provides additional evidence to reject 1-yr MDT for MB patients.

The issue of whether relapses in leprosy are due to reactivation of persisting organisms or to reinfection is unresolved to date. In fact, lepromatous patients regularly harbor viable persistent *M. leprae* following prolonged chemotherapy, in over half of patients treated with 10 or more years of dapsone ([41]) or 5 yrs of rifampin ([42]). In tuberculosis the technology to distinguish strain variability has been available now for several years; while the bulk of tuberculosis relapse in the inmunocompenent host has been established to be due to reactivation, there is a considerable percentage of relapses in AIDS patients that are, in fact, reinfection ([40]). In this regard, it is noteworthy that while BL patients may gain specific *M. leprae* immune-reactivity after effective chemotherapy, LL patients remain anergic ([6]). It is only now in leprosy that genetic polymorphisms amongst *M. leprae* strains have been detected ([18, 19, 28, 39]), and we currently examining this issue. If leprosy relapse is, in fact, reactivation, reinfection, or at times both, data on this issue should be soon available.

ALTERNATIVES TO 2-YEAR WHO-MDT FOR MB LEPROSY

Considerations for improving 2-yr WHO-MDT include: (i) extending the duration of MDT and/or adding an initial intensive phase of bactericidal therapy, (ii) the use of combinations of newer and more bactericidal drugs, and (iii) life-long therapy.

(i) In several locales, the duration of MDT has been extended and/or combined with the incorporation of an earlier, more intensive regimen and with improved relapse rates. In Agra ([17]), when patients with a pre-treatment BI of 4+ or greater were treated with 2-yr WHO-MDT a relapse rate of 17% was obtained, while when MDT was extended to smear negativity (on average 5 yrs) the relapse rate was reduced to 4%. In Malaysia, since 1986 the standard

regimen for MB leprosy has been initial hospitalization with daily observed therapy (including dapsone, clofazimine, rifampin) for 1 month, followed by WHO-MDT for 5 yrs. On this regimen, no relapses have been found in several hundred patients (personal communication, Majid, Azmon). In Bhutan, where many patients had been on dapsone monotherapy (some for prolonged times), patients were hospitalized and given daily dapsone and rifampin for 1 month, followed by dapsone alone for 1 yr . Unfortunately, follow-up of this experience is currently unavailable. In the early 1990s, the WHO embarked on a blinded comparative multi-centered trial of 4 regimens: (i) Daily rifampin and ofloxacin for one month, (ii) Regimen 1 follow ed by standard 1-yr WHO-MDT, (iii) 1-yr WHO-MDT, and (iv) 2-yr WHO-MDT. In Cebu, several early relapses were observed at one of the trial sites, particularly with Regimen 1. At least in Cebu, the 189 patients from that study have been on active annual follow-up for a long enough period that meaningful comparative relapse rates might become available. However, the WHO has not chosen to break the treatment code for late relapses in this study, making it impossible to determine the relative efficacy of the four treatment regimens, and it is not supporting the follow-up.

(ii) To date, only rifampin, dapsone, and clofazimine, the 3 components of WHO-MDT, have been utilized to any considerable extent to treat leprosy. Of these 3 antimicrobials, only rifampin has proved bactericidal in leprosy patients ([34, 38]). On the other hand, agents from 3 other classes of antimicrobials, tetracyclines (minocycline) ([7, 11, 14, 25, 26]), macrolides (clarithromycin) ([4, 9, 15, 25, 26]), and fluoroquinolones (pefloxacin and ofloxacin) ([8, 20, 21, 22, 30]) are bactericidal for *M. leprae* both in mice and leprosy patients. Though the WHO ([46]) has advocated single doses of rifampin, ofloxacin, and minocycline (ROM) for PB leprosy, and this has appeared ef fective in those with single lesions ([23]), combinations of these newer agents with rifampin in leprosy patients have not been tested to any considerable extent, and none with long term follow-up. Though Pattyn reported his previously described 4-drug regimen, 20% of patients relapsed ([32]). However, in that trial the duration of therapy was only 6 weeks and the regimen might have proved superior had it been maintained for a longer duration.

In the mouse model, there have been few studies comparing combinations of antimicrobials ([37]). One study ([16]) found that 2 and 3 drug combinations were generally additive or synergistic. Studies of regimens in the immunosuppressed, neonatally-thymectomized Lewis rat (NTLR) ([12]) appeared to be particularly useful in predicting which combinations might be especially ef fective in preventing relapse in MB patients. Heavily infected NTLR were treated with various antimicrobial combinations and evaluated for the presence of any persisting viable *M. leprae* one year after the completion of therapy by subsequent inoculation of both mice and NTLR. Several anti-microbial combinations appeared particularly effective, but only rifampin plus minocycline uniformly killed all *M. leprae*. Perhaps this combination deserves special attention.

(iii) Lifelong therapy for MB leprosy , principally dapsone monotherapy, was the norm and was highly successful for most of the latter half of the 20th Century. On dapsone monotherapy skin lesions resolved, neurologic deterioration ceased, patients became bacteriological negative and relapse, principally from dapsone-resistance organisms, was rare (2.5%) ([13, 29]). Dapsone monotherapy, moreover , is both inexpensive and has few side-effects, especially after the first few months of treatment. In certain locales drug supplies and long-term compliance are significant issues, but many patients, especially in the developed world, are on life-long medication for such things as diabetes mellitus hypertension, stroke prevention, hypercholesterolemia, gout, etc., wherein single daily doses of medication are found generally acceptable and ordinarily maintained. Why not consider lifelong therapy for a subset of MB patients?

REFERENCES

1. Becx Bleumink, M. Relapses among leprosy patients treated with multidrug therapy: experience in the leprosy control program of the All Africa Leprosy and Rehabilitation Training Center (ALERT) in Ethiopia; practical dif ficulties in diagnosing relapses; operational procedures and criteria for diagnosing relapses. Int. J. Lepr . Other Mycobact. Dis. **60** (1992) 421–435.

2. Blumberg, H. M., Burman, W. J., Chaisson, R. E., Daley, C. L., Etkind, S. C., Friedman, L. N., Fujiwara, P., Grzemska, M., Hopewell, P. C., Iseman, M. D., Jasmer, R. M., Koppaka, V., Menzies, R. I., O'Brien, R. J., Reves, R. R., Reichman, L. B., Simone, P. M., Starke, J. R., Vernon, A. A., The American Thoracic Society, Centers for Disease Control and Prevention, and The Infectious Diseases Society. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am. J. Respir. Crit. Care Med. **167(4)** (2003) 603–662.
3. Cellona, R. V., Balagon, M. V. F., Dela Cruz, E. C., Burgos, J. A., Abalos, R. M., Walsh, G. P., Topolski, R., Gelber, R. H., and Walsh, D. S. Long-term efficacy of 2-year WHO multiple-drug therapy (MDT) in multibacillary (MB) leprosy patients. Int. J. Lepr. Other Mycobact. Dis. **71** (2003) 308–319.
4. Chan, G. P., Garcia-Ignacio, B. Y., Chavez, V. E., Livelo, J. B., Jimenez, C. L., Parilla, M. L. R., and Franzblau, S. G. Clinical trial of clarithromycin for lepromatous leprosy. Antimicrob. Agents Chemother. **38** (1994) 515–517.
5. Chen, X., Li, W., Jiang, C., and Ye, G. Studies on risk of leprosy relapses in China: relapses after treatment with multidrug therapy. Int. J. Lepr. Other Mycobact. Dis. **67** (1999) 379–387.
6. Cree, I. A., Smith, W. C. S., Rees, R. J. W., and Swanson Beck, J. The influence of antimycobacterial chemotherapy on delayed hypersensitivity skin-test reactions in leprosy patients. Lepr. Rev. **59** (1988) 145–151.
7. Fajardo, T. T., Jr., Villahermosa, L. G., Dela Cruz, E. C., Abalos, R. M., Franzblau, S. G., and Walsh, G. P. Minocycline in Lepromatous Leprosy. Int. J. Lepr. Other Mycobact. Dis. **63** (1995) 8–17.
8. Fajardo, T. T., Jr., Villahermosa, L. G., Dela Cruz, E. C., Cellona, R. V., Balagon, M. V., Abalos, R. M., and Gelber, R. H. A clinical trial of pefloxacin and ofloxacin in lepromatous leprosy. Lepr. Rev. (2004) in press.
9. Franzblau, S. G., and Hastings, R. C. *In vitro* and *in vivo* activities of macrolides against *Mycobacterium leprae*. Antimicrob. Agents and Chemother. **32** (1988) 1758–1762.
10. Gebre, S., Saunderson, P., and Byass, P. Relapses after fixed duration multiple drug therapy: the AMFES cohort. Lepr. Rev. **71** (2000) 325–351.
11. Gelber, R. H. Activity of minocycline in *Mycobacterium leprae*-infected mice. J. Inf. Dis. **156** (1987) 236–239.
12. Gelber, R. H. Chemotherapy of lepromatous leprosy: recent developments and prospects for the future. Eur. J. Clin. Microbiol. Infect. Dis. **13** (1994) 942–952.
13. Gelber, R. H. U.S.-Japan Cooperative Medical Science Program Workshop on Leprosy Chemotherapy. Int. J. Lepr. Other Mycobact. Dis. **44** (1976) 369–373
14. Gelber, R. H., Fukuda, K., Byrd, S., Murray, L. P., Siu, P., Tsang, M., and Rea, T. H. A clinical trial of minocycline in lepromatous leprosy. British Med. J. **304** (1992) 91–92.
15. Gelber, R. H., Siu, P., Tsang, M., and Murray, L. P. Activities of various macrolide antibiotics against *Mycobacterium leprae* infection in mice. Antimicrob. Agents and Chemother. **35** (1991) 760–763.
16. Gelber, R. H., Siu, P., Tsang, M., Richard, V., Chehl, S., and Murray, L. Activity of combinations of dapsone, rifampin, minocycline, clarithromycin, and sparfloxacin against *M. leprae*-infected mice. Int. J. Lepr. Other Mycobact. Dis. **63** (1995) 259–264.
17. Girdhar, B. K., Girdhar, A., and Kumar, A. Relapses in multibacillary leprosy patients: effect of length of therapy. Lepr. Rev. **71** (2000) 144–153.
18. Groathouse, N., Rivoire, B., Cho, S., Kim, H., Lee, H., Brennan, P., and Vissa, V. D. Polymorphisms in short tandem repeat sequences of *Mycobacterium leprae* allow for the epidemiological characterization of strains. Int. J. Lepr. Other Mycobact. Dis. **71** (2003) 379–380.
19. Groathouse, N. A., Rivoire, B., Kim, H., Lee, H., Cho, S. N., Brennan, P. J., and Vissa, V. D. Multiple polymorphic loci for molecular typing of *Mycobacterium leprae* strains. J. Clin. Microbiol. (In Press)
20. Grosset, J. H., Guelpa-Lauras, C. C., Perani, E. G., and Beoletto, C. Activity of ofloxacin against *Mycobacterium leprae* in the mouse. Int. J. Lepr. Other Mycobact. Dis. **56** (1988) 259–264.
21. Grosset, J. H., Ji, B., Guelpa-Lauras, C. C., Perani, E. G., and N'Deli, L. N. Clinical trial of pefloxacin and ofloxacin in the treatment of lepromatous leprosy. Int. J. Lepr. Other Mycobact. Dis. **58** (1990) 281–295.
22. Guelpa-Lauras, C. C., Perani, E. G., Giroir, A. M., and Grosset, T. H. Activity of pefloxacin and ciprofloxacin against *Mycobacterium leprae* in the mouse. Int. J. Lepr. Other Mycobact. Dis. **55** (1987) 70–77.
23. Gupte, M. D. Field trials of a single dose of the combination rifampicin-ofloxacin-minocycline (ROM) for the treatment of paucibacillary leprosy. Lepr. Rev. **71(Suppl)** (2000) S77–S80.
24. Jamet, P., and Ji, B. Relapse after long-term follow up of multibacillary patients treated by WHO multidrug regimen. Marchoux Chemotherapy Study Group. Int. J. Lepr. Other Mycobact. Dis. **63** (1995) 195–201.
25. Ji, B., Jamet, P., Perani, E. G., Bobin, P., and Grosset, J. H. Powerful bactericidal activities of clarithromycin and minocycline against *Mycobacterium leprae* in lepromatous leprosy. J. Infect. Dis. **168** (1993) 188–190.
26. Ji, B., Perani, E. G., and Grosset, J. H. Effectiveness of clarithromycin and minocycline alone

or in combination against experimental *Mycobacterium leprae* infection in mice. Antimicrob. Agents Chem. **35** (1991) 579–581.

27. Li, H., Hu, L., Huang, W., Liu, G., Yuan, I., Jin, Z., Li, X., and Yang, Z. Risk of relapse in leprosy after fixed duration multidrug therapy. Int. J. Lepr. Other Mycobact. Dis. **65** (1997) 238–245.
28. Matsuoka, M., Maeda, S., Kai, M., Nakata, N., Chae, G. T., Gillis, T. P., Kobayashi, K., Izumi, S., and Kashiwabara, Y. *Mycobacterium leprae* typing by genomic diversity and global distribution of genotypes. Int. J. Lepr . Other Mycobact. Dis. **68** (2000) 121–128.
29. Meade, T. W., Pearson, J. M. H., Rees, R. J. W., and North, W. R. S. The epidemiology of sulphone resistant leprosy. Bergen: Abstract Tenth International Leprosy Congress, 1973. p. 332.
30. N'Deli, L., Guelpa-Lauras, C. C., Perani, E. G., and Grosset, J. H. Effectiveness of pefloxacin in the treatment of lepromatous leprosy. Int. J. Lepr. Other Mycobact. Dis. **58** (1990) 23–28.
31. Norman, G., Joseph, G., and Richard, J. Relapses in multibacillary patients treated with multi-drug therapy until smear negativity: Findings after twenty years. Int. J. Lepr . Other Mycobact. Dis. **72** (2004) 1–7.
32. Pattyn, S., and Grillone, S. Relapse rates and a 10-year follow-up of a 6-week quadruple drug regimen for multibacillary leprosy. Lepr. Rev. **73** (2002) 245–247.
33. Program Kawalan Kusta Negara. Kuala Lumpur, Malaysia, 1997.
34. Rees, R. J. W., Pearson, J. M. H., and Waters, M. F. R. Experimental and clinical studies on rifampicin in treatment of leprosy . Brit. Med. J. **1** (1970) 89–92.
35. Shaw, I. N., Christian, M., Jesudasan, K., Kurian, N., and Rao, G. S. Effectiveness of multidrug therapy in multibacillary leprosy: a long term follow-up of 34 multibacillary leprosy patients treated with multidrug regimens till smear negativity. Lepr. Rev. **74** (2003) 141–147.
36. Shaw, I. N., Natarajan, M., Rao, G. S., Jesudasan, K., Christian, M., and Kavitha, M. Long-term follow-up of multibacillary leprosy patients with high BI treated with WHO/MDT regimen for a fixed duration of two years. Int. J. Lepr. Other Mycobact. Dis. **68** (2000) 405–409.
37. Shepard, C. C. Combinations involving dapsone, rifampin, clofazimine, and ethionamide in the treatment of *M. leprae* infections in mice. Int. J. Lepr. Other Mycobact. Dis. **44** (1976) 135–139.
38. Shepard, C. C., Levy, L., and Fasal, P. Rapid bactericidal ef fect of rifampicin on *M. leprae* . Amer. J. Trop. Med. Hyg. **21** (1972) 446–449.
39. Shin, Y. C., Lee, H., Walsh, G. P., Kim, J. D., and Cho, S. N. Variable numbers of TTC repeats in *Mycobacterium leprae* DNA from leprosy patients and use in strain differentiation. J. Clin. Microbiol. **38** (2000) 4535–4538.
40. Small, P. M., Shafer, R. W., Hopewell, P. C., Singh, S. P., Murphy, M. J., Desmond, E., Sierra, M. F., and Schoolnik, G. K. Exogenous reinfection with multidrug-resistant *Mycobacterium tuberculosis* in patients with advanced HIV infection. N. Engl. J. Med. **328** (1993) 1137–1144.
41. Waters, M. F. R., Rees, R. J. W., McDougall, A. C., and Weddell, A. G. M. Ten years of dapsone in lepromatous leprosy: clinical, bacteriological and histological assessment and the findings of viable leprosy bacilli. Lepr. Rev. **45** (1974) 288–298.
42. Waters, M. F. R., Rees. R. J. W., Pearson, J. M. H., Laing, A. B. G., Helmy, H. S., and Gelber, R. H. Rifampicin for lepromatous leprosy: nine years' experience. Brit. Med. J. **1** (1978) 133–136.
43. World Health Organization. Report on Fourth meeting. WHO Technical Advisory Group on Elimination of Leprosy. Geneva: WHO, 2002.
44. World Health Organization. Report on Sixth Meeting. WHO Technical Advisory Group on Elimination of Leprosy. Geneva: WHO, 2004.
45. World Health Organization. Risk of relapse in leprosy. The Leprosy Unit. Division of Tropical Diseases, 94.1. Geneva: World Health Organization, 1994.
46. WHO Expert Committee on Leprosy. Seventh report. Geneva: World Health Organization, 1998. Tech. Rep. Ser., No. 874