Lepr Rev (2008) **79,** 353–357

EDITORIAL

Evidence based practice in leprosy: where do we stand?

NATASJA H.J. VAN VEEN &
JAN HENDRIK RICHARDUS
Department of Public Health, Erasmus MC, University Medical Center Rotterdam, PO Box 2040, 3000CA, The Netherlands

Accepted for publication 02 December 2008

What is Evidence Based Medicine?

Since the 1990s, the concept of 'evidence based medicine' (EBM) has received growing interest. Its main rationale was the recognition that systematic synthesis of evidence from high quality clinical research should be guiding clinical practice. Important developments in EBM included the introduction of structured abstracts and of systematic reviews.[1] Nowadays, EBM can be described as 'healthcare practice that is based on integrating knowledge gained from the best available research evidence, clinical expertise, and patients' values and circumstances'.[2] While results from randomised controlled trials (RCTs), and especially the systematic review of several RCTs, are often considered as 'best evidence', RCTs are not suitable for all types of clinical questions, such as assessing the accuracy of diagnostic tests or the impact of prognostic factors. Evidence based medicine should therefore not be limited to RCTs and meta-analyses. Its main goal is to guide clinical decision making that is based on the best available evidence.[2,3]

Whether EBM has made a difference in the past decade was discussed in a special theme issue of the *British Medical Journal* (October 30, 2004). EBM has made a difference in contributing to the discussion and development of systematically collecting and summarising evidence of clinical research. EBM has not only created enthusiasm, but has also received criticism. For example, critics opposed the idea that EBM would restrict choices in terms of promoting a single 'right' way to practice, would declare RCTs as the only type of study to be useful, or would be driven by costs and cost savings.[2] One of the big challenges for EBM in the coming years will be to implement clinical evidence into clinical practice. EBM should not only produce best available evidence, but should also find effective ways for implementation and to make this evidence accessible to clinicians, consumers, policy makers, and other stakeholders.[2,4,5]

Correspondence to: Jan Hendrik Richardus (e-mail: j.richardus@erasmusmc.nl)

0305-7518/08/064053+05 $1.00

Evidence from Clinical and Epidemiological Studies in Leprosy

Publication of clinical studies in leprosy dates back to the early 1950s when dapsone was introduced for the treatment of leprosy, and immune-suppressant drugs for the management of leprosy reactions were examined. Over the years much research has been conducted in the field of leprosy, gradually contributing to our knowledge base. Many clinical studies however, were small-scale and often did not fulfil the rigorous methodological criteria that we have become accustomed to in clinical practice over the past two decades.

Among the first larger multicentre randomised controlled trials (RCTs) were the THELEP trials (1977–1983), which examined five multidrug regimens in 215 untreated multibacillary leprosy (MB) patients. The results gave strong support to the intermittent, rifampicin-containing regimen (MDT) recommended by the WHO Study Group on Chemotherapy for Leprosy Control for the treatment MB leprosy.[6] Clinical trials were also undertaken to establish the value of a single-dose combination of rifampicin, ofloxacin and monocycline (ROM) to treat paucibacillary leprosy.[7] The follow-up of these trials has unfortunately been poor. Recently, an international open trial was started of a uniform multi-drug therapy regimen for 6 months for all types of leprosy patients.[8]

In the late 1980s and 1990s large prospective cohort studies were conducted, such as the ALERT MDT Field Evaluation Study (AMFES),[9–12] and the Bangladesh Acute Nerve Damage Study (BANDS).[13–15] These studies were instrumental in describing the incidence of nerve function impairment (NFI) and in identifying risk factors and prognostic factors for nerve damage. An important off-shoot of BANDS was the development of a clinical prediction rule for NFI in leprosy patients.[16,17] The abundant data from these studies were used to develop three multicentre RCTs in prevention of disability in leprosy (TRIPOD).[18–20] The trials, which started in 1998, examined the effects of prophylactic corticosteroids in preventing NFI, and of corticosteroids for treating mild and long-standing NFI. In 1999 a new study was designed because of remaining questions regarding underlying mechanisms of neuropathy, treatment of acute and recurrent nerve damage and reactions, and early diagnosis of nerve damage. This was the International Nerve Function Impairment and Reaction (INFIR) study, a prospective multicentre cohort study investigating prediction, detection and pathogenesis of peripheral neuropathy and reactions in leprosy.[21–23]

After studies of chemoprophylaxis with dapsone in the 1970s in India,[24] and in the 1990s with ROM in Micronesia,[25] a large RCT on chemoprophylaxis (a single dose of rifampicin) for contacts of leprosy patients was initiated in 2002 in Bangladesh, the study on contact transmission and chemoprophylaxis in leprosy (COLEP).[26,27] The results of this study are expected to be the basis for possible recommendations regarding the implementation of chemoprophylactic strategies in leprosy control in future.

Evidence from Systematic Reviews in Leprosy

We performed three Cochrane reviews to systematically evaluate the best available information and evidence for interventions to treat nerve damage and reactions in leprosy. Two reviews assessed the effects of corticosteroids and decompressive surgery for treating nerve damage in leprosy, respectively.[28,29] In this issue of *Leprosy Review* a shortened Cochrane review on the role of corticosteroids in treating nerve damage is published. The third Cochrane review, which is in progress, examines the effects of interventions to treat

ENL.[30] Recently another Cochrane review has also been published on interventions for skin changes caused by nerve damage in leprosy.[31]

While Cochrane reviews focus on evidence from RCTs, we anticipated that only a few RCTs had been conducted in the area of treating nerve damage and its consequences. Indeed, there were only three trials available involving 513 people on corticosteroids and two trials involving 88 people on decompressive surgery. None of the trial results could be combined in a meta-analysis and we could not draw any robust conclusions about the effectiveness of these interventions for treating nerve damage in leprosy, especially on the longer-term. The Cochrane review on interventions for skin changes assessed the effects of self-care, dressings and footwear in preventing and healing secondary damage to the skin in persons affected by leprosy. In this review eight trials with a total of 557 participants were included and it was concluded that there is a lack of high quality research in the field of ulcer prevention and treatment in leprosy.[31] In all Cochrane reviews the results of non-randomised studies were discussed, since they may confirm evidence from RCTs or provide 'second best' available evidence, especially if the studies were properly designed and conducted.

Evidence Based Medicine in Leprosy Practice

Evidence from research has certainly led to better practice in leprosy control. The introduction of MDT has been a great step forward in reducing the number of people with leprosy, and identification of risk factors and prognostic factors of NFI has led to improved diagnosis and monitoring of patients. But sometimes it is unclear whether practice has been guided by best evidence or any evidence from research at all, as illustrated by the recommendations with respect to MDT treatment, especially for MB patients. In 1981, the WHO recommended a minimum of 2 years treatment for MB patients, which was shortened to 24 months in 1994 and later further shortened to the currently recommended 12 months.[32] Relapse rates are acceptably low with the 24-month treatment.[33] There is no evidence however, to support the shortened duration of treatment to 12 months for MB patients. On the contrary, published data show an increased risk of relapse in the long-term for patients with high bacterial loads.[34–35] Changes in guidelines or recommendations should be based on evidence from well-conducted research to maintain effective leprosy control.[36,37] Recently, the ILEP published a report with evidence-based graded recommendations on different aspects of leprosy control, diagnosis and treatment.[38]

Conclusion

While the importance and value of evidence based medicine (EBM) and of well-designed RCTs have been acknowledged within the leprosy research and medical community, some may still misunderstand the concept of EBM or worry about the 'superiority' of RCTs or systematic reviews compared to non-randomised studies or clinical experience. But EBM is not restricted to RCTs because many clinical questions cannot or need not be answered by a RCT (e.g. accuracy of diagnostic tests, the power of prognostic factors). And when evidence of RCTs is lacking, one should identify and assess the next best available evidence. We can conclude that evidence based practice in leprosy has improved in recent years and that the concept of EBM is becoming more accepted and established. On the other hand, there is still

much need for improvement in conducting clinical research in leprosy. Evidence from good research is essential for good clinical practice, but it should guide, not dictate, clinical practice. Evidence based medicine must lead to practice where the best available research evidence, clinical experience and patient's values go hand in hand to achieve the best care and cure for individual patients.

References

[1] Guyatt G, Cook D, Haynes B. Evidence based medicine has come a long way. *BMJ*, 2004; **329**(7473): 990–991.
[2] Dickersin K, Straus SE, Bero LA. Evidence based medicine: increasing, not dictating, choice. *BMJ*, 2007; **334**(Suppl 1): s10.
[3] Sackett DL, Rosenberg WM, Gray JA *et al.* Evidence based medicine: what it is and what it isn't. *BMJ*, 1996; **312**(7023): 71–72.
[4] Reilly BM. The essence of EBM. *BMJ*, 2004; **329**(7473): 991–992.
[5] Straus SE, Jones G. What has evidence based medicine done for us? *BMJ*, 2004; **329**(7473): 987–988.
[6] Levy L. *The THELEP controlled clinical trials in lepromatous leprosy* World Health Organization, Geneva, 1999.
[7] Gupte MD. Field trials of a single dose of the combination rifampicin-ofloxacin-minocycline (ROM) for the treatment of paucibacillary leprosy. *Lepr Rev*, 2000; **71**(Suppl): S77–S80.
[8] Kroger A, Pannikar V, Htoon MT *et al.* International open trial of uniform multi-drug therapy regimen for 6 months for all types of leprosy patients: rationale, design and preliminary results. *Trop Med Int Health*, 2008; **13**: 594–602.
[9] Saunderson P, Gebre S, Desta K *et al.* The pattern of leprosy-related neuropathy in the AMFES patients in Ethiopia: definitions, incidence, risk factors and outcome. *Lepr Rev*, 2000; **71**: 285–308.
[10] Meima A, Saunderson PR, Gebre S *et al.* Factors associated with impairments in new leprosy patients: the AMFES cohort. *Lepr Rev*, 1999; **70**: 189–203.
[11] Saunderson P, Gebre S, Byass P. ENL reactions in the multibacillary cases of the AMFES cohort in central Ethiopia: incidence and risk factors. *Lepr Rev*, 2000; **71**: 318–324.
[12] Meima A, Saunderson PR, Gebre S *et al.* Dynamics of impairment during and after treatment: the AMFES cohort. *Lepr Rev*, 2001; **72**: 158–170.
[13] Croft RP, Richardus JH, Nicholls PG, Smith WC. Nerve function impairment in leprosy: design, methodology, and intake status of a prospective cohort study of 2664 new leprosy cases in Bangladesh (The Bangladesh Acute Nerve Damage Study). *Lepr Rev*, 1999; **70**: 140–159.
[14] Nicholls PG, Croft RP, Richardus JH *et al.* Delay in presentation, an indicator for nerve function status at registration and for treatment outcome–the experience of the Bangladesh Acute Nerve Damage Study cohort. *Lepr Rev*, 2003; **74**: 349–356.
[15] Richardus JH, Nicholls PG, Croft RP *et al.* Incidence of acute nerve function impairment and reactions in leprosy: a prospective cohort analysis after 5 years of follow-up. *Int J Epidemiol*, 2004; **33**: 337–343.
[16] Croft RP, Nicholls PG, Steyerberg EW *et al.* A clinical prediction rule for nerve-function impairment in leprosy patients. *Lancet*, 2000; **355**(9215): 1603–1606.
[17] Schuring RP, Richardus JH, Steyerberg EW *et al.* Preventing nerve function impairment in leprosy: validation and updating of a prediction rule. *PLoS Negl Trop Dis*, 2008; **2**: e283.
[18] Smith WC, Anderson AM, Withington SG *et al.* Steroid prophylaxis for prevention of nerve function impairment in leprosy: randomised placebo controlled trial (TRIPOD 1). *BMJ*, 2004; **328**(7454): 1459.
[19] Van Brakel WH, Anderson AM, Withington SG *et al.* The prognostic importance of detecting mild sensory impairment in leprosy: a randomized controlled trial (TRIPOD 2). *Lepr Rev*, 2003; **74**: 300–310.
[20] Richardus JH, Withington SG, Anderson AM *et al.* Treatment with corticosteroids of long-standing nerve function impairment in leprosy: a randomized controlled trial (TRIPOD 3). *Lepr Rev*, 2003; **74**: 311–318.
[21] van Brakel WH, Nicholls PG, Das L *et al.* The INFIR Cohort Study: investigating prediction, detection and pathogenesis of neuropathy and reactions in leprosy. Methods and baseline results of a cohort of multibacillary leprosy patients in north India. *Lepr Rev*, 2005; **76**: 14–34.
[22] van Brakel WH, Nicholls PG, Wilder-Smith EP *et al.* Early diagnosis of neuropathy in leprosy-comparing diagnostic tests in a large prospective study (the INFIR Cohort Study). *PLoS Negl Trop Dis*, 2008; **2**: e212.
[23] Marlowe SN, Hawksworth RA, Butlin CR *et al.* Clinical outcomes in a randomized controlled study comparing azathioprine and prednisolone versus prednisolone alone in the treatment of severe leprosy type 1 reactions in Nepal. *Trans R Soc Trop Med Hyg*, 2004; **98**: 602–609.
[24] Noordeen SK. Prophylaxis–scope and limitations. *Lepr Rev*, 2000; **71**(Suppl): S16–S19; Discussion S9–20.
[25] Diletto C, Blanc L, Levy L. Leprosy chemoprophylaxis in Micronesia. *Lepr Rev*, 2000; **71**(Suppl): S21–S23; Discussion S4–5.

[26] Moet FJ, Oskam L, Faber R *et al.* A study on transmission and a trial of chemoprophylaxis in contacts of leprosy patients: design, methodology and recruitment findings of COLEP. *Lepr Rev*, 2004; **75**: 376–388.
[27] Moet FJ, Pahan D, Oskam L *et al.* Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. *BMJ*, 2008; **336**(7647): 761–764.
[28] Van Veen NH, Nicholls PG, Smith WC, Richardus JH. Corticosteroids for treating nerve damage in leprosy. *Cochrane Database Syst Rev*, 2007; : CD005491.
[29] van Veen NHJ, Schreuders TAR, Theuvenet WJ, *et al.* Decompressive surgery for treating nerve damage in leprosy. *Cochrane Database Syst Rev* (accepted).
[30] van Veen NHJ, Lockwood DNJ, van Brakel WH *et al.* Interventions for erythema nodosum leprosum. *(Protocol) Cochrane Database Syst Rev*, 2008; : CD006949.
[31] Reinar LM, Forsetlund L, Bjorndal A, Lockwood D. Interventions for skin changes caused by nerve damage in leprosy. *Cochrane Database Syst Rev*, 2008; : CD004833.
[32] World Health Organization. WHO Expert Committee on Leprosy. *World Health Organ Tech Rep Ser*, 1998; **874**: 1–43.
[33] Lockwood D. Leprosy. *Clin Evid*, 2002; **8**: 709–720.
[34] Girdhar BK, Girdhar A, Kumar A. Relapses in multibacillary leprosy patients: effect of length of therapy. *Lepr Rev*, 2000; **71**: 144–153.
[35] Baohong J. Does there exist a subgroup of MB patients at greater risk of relapse after MDT? *Lepr Rev*, 2001; **72**: 3–7.
[36] Lockwood DN, Kumar B. Treatment of leprosy. *BMJ*, 2004; **328**(7454): 1447–1448.
[37] Lockwood DN. Leprosy elimination-a virtual phenomenon or a reality? *BMJ*, 2002; **324**(7352): 1516–1518.
[38] ILEP. Report of the International Leprosy Association Technical Forum 2002. London; 2002.