Lepr Rev (1998) **69,** 222–224

Editorial

MYCOBACTERIUM W IMMUNOTHERAPY IN LEPROSY

Recent trials which demonstrate the benefits of BCG vaccination in preventing all types of leprosy have been followed by trial reports suggesting that immunotherapy may have a role in the treatment of leprosy patients. Extremely thorough work in India identifying, purifying and bringing to trial autoclaved *Mycobacterium w* (M.w.) has been rewarded with very encouraging early trial results from pilot studies[1] and the first relatively small unblinded trials.[2–4] However, there remain a number of important questions to be answered before the role of M.w. can be clearly defined and it can be recommended for routine clinical practice.

WHO multi-drug therapy has proved highly effective in curing bacterial disease, both pauci- and multibacillary cases, with very few relapses. However, treatment of multibacillary cases lasts at least 12 months and complications of reversal reactions, neuritis and erythema nodosum leprosum (ENL) are common, unpleasant, and difficult to treat in many cases. Thus there is most interest in the effects of M.w. on the multibacillary group, for whom a shortening of the duration of treatment, or a reduction in reactions, or a reduction in long-term disability would be very important contributions.

The rationale for immunotherapy with *Mycobacterium w* (M.w.) is that it may boost cell-mediated immunity and therefore lead to increased clearance of bacilli. The published reports comparing vaccinated and unvaccinated individuals seem to confirm that this happens, with Bacterial Index (BI) and viability of *M. leprae* in mouse footpad testing falling more rapidly in BB, BL and LL patients vaccinated with M.w. analysed separately.[5,6] Subgroup analysis should be interpreted cautiously because of small numbers, but the effect is least clear-cut in the LL cases. This is made less easy to interpret because the vaccinated groups started with lower BIs, but is convincing, nevertheless. BCG also seems to cause the same effect[5]. Lepromin conversion rates are higher in those given immunotherapy. These studies of surrogate markers suggest the theoretical basis behind immunotherapy is sound, but does this translate into significant clinical improvement?

The problems with measuring clinical outcome in leprosy are well known, and no scoring system is ideal. Published studies used two outcomes. One was a clinical score (first described by Ramu[7]); the other was release from treatment. Neither is 'objective' (for example fever/no fever or dead/alive); both depend on the assessment of a clinician. It is therefore essential, if they are to be entirely reliable, that there should be double blinding of the highest possible standard. The early studies were unblinded, or semi-blinded; the study reported by Zaheer *et al.* was described as double-blind. This is exceptionally difficult in the case of M.w., as active vaccination causes local induration and erythema, then the formation of a well defined

 0305-7518/98/069222+03 $1.00

ulcer, with scar formation from about 3 weeks. Blinding the patient is therefore effectively impossible, and clinicians, who must perform careful examination of the skin both for the scoring system and to decide on release from treatment, will be given a strong hint by the presence or absence of a recent typical scar. Where clinicians believe in a treatment, it is almost impossible not to be influenced by this, albeit unconsciously. The use of plasters on all upper arms to hide scars or lack of scars was used in some trials of BCG where similar problems exist, and those conducting M.w. trials might want to consider this. With this caveat, the first trials are encouraging, with quicker apparent resolution for all multibacillary cases, both in improvement of clinical score and in release from treatment.

The overall bacteriological cure in multibacillary leprosy is unlikely to be significantly improved by immunotherapy, as it is already close to 100% with conventional treatment even in field conditions. It is also unlikely to make any impact on transmission, since cases are non-infectious within 48 h of starting conventional treatment, and almost all transmission occurs before cases are identified or treated at all—hopes that it will 'provide a big boost in the leprosy eradication campaign[8], are therefore misplaced. However, a faster resolution is definitely in the interests of patients, and has clear operational advantages provided it does not carry a heavy price. If immunotherapy does kick-start the cell-mediated immune system to recognize the bacilli and kill them earlier in the disease than conventional treatment, it may hasten bacterial clearance, but at the risk of causing a higher incidence of immune-mediated reactions. These can be very unpleasant and potentially cause life-long disability. Preventing and managing ENL, neuritis and other immune-mediated problems remains one of the great challenges in leprosy, and is often only partially successful. There are theoretical reasons for thinking successful immunotherapy might cause a higher incidence of these problems (and some which might suggest the reverse): the question is—does it? At present, the evidence of this is mixed, but there are serious concerns which will need addressing before immunotherapy can be wholeheartedly recommended.

The early studies were not large enough to detect anything but the grossest evidence of increased reactions, and were not designed to do so. The abstracts of two studies which do address the problem of type 1 reactions give the impression that there was no important difference in rates of reaction between vaccinated and unvaccinated groups, but the data give a less reassuring picture. One study set out to look specifically at this question.[9] This found a 22·6% incidence of reversal reaction in the vaccine group ($n = 53$) and 15% in the control group ($n = 53$), with more severe reactions in the vaccinated group. Only three patients had neuritis—two in the vaccine group, one in the control group. This failed to achieve statistical significance and was reported as showing no evidence of increased neurological damage. However, since there were only 53 patients in each arm, there was little chance of achieving significance, and the failure to prove a difference did not prove that no difference exists.[10] A larger study by the same group was reported by Zaheer *et al.*, with 93 vaccinated patients and 107 controls.[6] This also demonstrated more type 1 reactions, with 35% of vaccinated patients having reactions and only 17% of controls, the difference being most marked in the LL patients. On the other hand, they report fewer episodes of neuritis and ENL in the vaccinated groups, although some of the figures are puzzling, in particular the fact that more LL controls are reported as having neuritis (70) than there are patients in the LL control group (68).

The apparent increase in type 1 reactions and the absence of any long-term follow up data on the very important endpoints of relapse and disability make it inappropriate for immunotherapy with M.w. to be recommended in routine clinical practice at present. Initial

excitement is understandable, but over-hyping M.w. at this stage is unhelpful for patients and those administering programmes on the ground. Properly blinded randomized trials which are large enough to pick up significant differences, particularly in neuritis and long-term disability, will need to be reported before the place of M.w. becomes clear. Further studies are underway in India, and the initial results are sufficiently encouraging that trials in different ethnic groups and settings are warranted at this stage. Meanwhile immunotherapy should only be given in the context of a properly conducted trial. Everybody treating patients with multibacillary leprosy will hope that immunotherapy lives up to its initial promise of faster cure without increased harm, but the case for it is not yet proved.

Hospital for Tropical Diseases
4 St Pancras Way
London NW1 0PE, UK

CHRISTOPHER WHITTY

References

[1] Chaudhuri S, Fotedar A, Talwar GP. Lepromin conversion in repeatedly lepromin negative BL/LL patients after immunization with autoclaved *Mycobacterium w*. *Int J Lepr*, 1983; **51:** 159–168

[2] Talwar GP, Zaheer SA, Mukherjee R, Walia R, Misra RS, Sharma AK *et al*. Immunotherapeutic effects of a vaccine based on a saprophytic cultivable mycobacterium, *Mycobacterium w* in multibacillary leprosy patients. *Vaccine*, 1990; **8:** 121–129.

[3] Zaheer SA, Mukherjee R, Ram Kumar B, Misra RS, Sharma AK, Kar HK. Combined multidrug and *Mycobacterium w* vaccine therapy in patients with multibacillary leprosy. *J Infect Dis*, 1993; **167:** 401–410.

[4] Natarajan M, Katoch K, Bagga AK, Katoch VM. Histological changes with combined chemotherapy and immunotherapy in highly bacillated lepromatous leprosy. *Acta Leprol*, 1992; **8:** 79–86.

[5] Katoch K, Katoch VM, Natrajan M, Bhatia AS, Sreevesa, Gupta UD *et al*. Treatment of bacilliferous BL/LL cases with chemotherapy and immunotherapy. *Int J Lepr*, 1995; **63:** 201–212.

[6] Zaheer SA, Beena KR, Kar HK, Sharma AK, Misra RS, Mukherjee A. *et al*. Addition of immunotherapy with *Mycobacterium w* vaccine to multi-drug therapy benefits multibacillary leprosy patients. *Vaccine*, 1995; **13:** 1102–1110.

[7] Ramu G, Desikan KV. A follow up study of borderline tuberculoid leprosy under sulphone monotherapy. *Ind J Lepr*, 1988; **60:** 26–33.

[8] Mudur G. 'India approves leprosy vaccine' News section. *BMJ*, 1998; **316:** 414.

[9] Kar HK, Sharma AK, Misra RS, Beena KR, Zaheer SA, Mukherjee R *et al*. Reversal reaction in multibacillary leprosy patients following MDT with and without immunotherapy with a candidate vaccine for an antileprosy vaccine, *Mycobacterium w*. Lepr Rev 1993; **64:** 219–226.

[10] van Brakel WH. Comment: reversal reaction in multibacillary leprosy patients following MDT with and without immunotherapy with a candidate vaccine for an antileprosy vaccine, *Mycobacterium w*. *Lepr Rev* 1994; **65:** 404–405.