Preventing Leprosy: Epidemiological and immunological aspects of chemo- and immunoprophylaxis in leprosy patients' contacts

Richardus, R.A.

SUMMARY

Leprosy is an infectious disease caused by *Mycobacterium leprae (M. leprae)*, which can cause damage to the skin and peripheral nerves. The global number of new leprosy patients has remained constant over the past decennium, with a total number of around 200,000 of which 10% are children. This indicates that transmission of *Mycobacterium leprae* is ongoing in many endemic countries. People living in the same household as untreated leprosy cases have the highest risk of infection with *M. leprae* and developing disease. Therefore, it is essential that leprosy control strategy is focused on this risk group. This strategy has three basic pillars: 1) identifying new leprosy patients; 2) treating new leprosy patients; and 3) treating contacts of new leprosy patients.

In the past years, several studies have investigated the use of immunoprophylaxis (vaccination) and chemoprophylaxis (medication) to prevent the spread of leprosy among contacts of leprosy patients. Bacillus Calmette-Guérin (BCG) is the most frequently given vaccine in the world. It is known as a vaccine against tuberculosis and is routinely given to infants in countries endemic for tuberculosis as part of the neonatal immunization. BCG is also recognized as protecting against leprosy. In Brazil, the government officially recommends BCG (re)vaccination as prophylaxis to protect household contacts of newly diagnosed leprosy cases. This policy showed a 56% protection rate in a Brazilian cohort study. However, a high number of new leprosy patients were found amongst the contacts in the first 2-10 months after BCG vaccination.

The COLEP trial, performed in the northwest of Bangladesh between 2002 and 2009, showed that the use of a single dose of the antibiotic rifampicin (SDR) as chemoprophylaxis in contacts of new leprosy patients reduced the incidence of leprosy in the first two years after intake with 57% compared to placebo; after four and six years no additional effect was seen. BCG vaccination and SDR each had a protective effect in contacts of around 60%, but the COLEP study also showed an additional additive protective effect of SDR (80%) in contacts that had received BCG vaccination in the past.

Based on the experience with BCG vaccination and SDR chemoprophylaxis in preventing leprosy among contacts of leprosy patients, a trial was started in Bangladesh to assess the efficacy of a combined strategy (the MALTALEP study). The MALTALEP study is a cluster randomized controlled trial in the northwest of Bangladesh between 2012 and 2018, in which around 15,000 contacts of newly diagnosed leprosy patients received either BCG alone, or BCG plus SDR. The primary outcome was the development of leprosy within two years after receiving BCG with or without SDR.

Chapter 1 gives a general introduction to the thesis. Chapter 2 describes how the blood of symptom-free contacts of new leprosy patients of the COLEP study was collected and analyzed at three time points over a period of six years. This showed that the anti-PGL-I antibody rates at intake did not significantly differ between contacts that developed leprosy during the study and those that remained symptom-free. Also, the presence of anti-PGL-I antibodies could not predict leprosy in this population, since no significant correlation was found between anti-PGL-I antibody rates at intake and when leprosy was developed. Chapter 3 of this thesis describes the methods section of the MALTALEP trial.

In Chapter 4 we described 21 contacts of new leprosy patients who developed PB leprosy within 12 weeks after BCG vaccination (0,4% of vaccinated contacts). This relatively high percentage is possibly caused by stimulation of the cell-mediated immunity by homologues of *M. leprae* proteins (antigens) in BCG. When BCG is given to contacts who have previously been exposed to *M. leprae*, this stimulates an immune reaction that may give rise to clinical leprosy.

In Chapter 5 we described the adverse events that occurred amongst contacts that had received BCG (in 0,34% of vaccinated contacts), which consisted mainly of skin ulcers. Comparable to the pathological T-cell immunity in PB leprosy patients, contacts with adverse events had elevated Th1 rates in reaction to *M. leprae* specific proteins in whole blood assays. However, for serum proteins associated with T cell regulation, lower levels were found in reaction to *M. leprae* antigens, possibly pointing to uncontrolled T-cell immunity that destroys the skin.

Chapter 6 describes the results of the MALTALEP trial. SDR reduced the number of new PB leprosy cases amongst contacts that had been vaccinated with BCG with 42%. Unfortunately, this effect is not significant, because the number of new leprosy patients was too low. Also, a large proportion of the new leprosy patients (33.6%) arose between 8-12 weeks after BCG vaccination, the time frame between vaccination and SDR. Therefore, it is difficult to say if SDR can suppress the augmentation of new leprosy patients amongst contacts in the first year after BCG. Based on this study, we cannot advise the introduction of BCG followed by SDR as a routine intervention to prevent the spread of leprosy. SDR as chemoprophylaxis, however, has been become part of the guidelines of the WHO, because monotherapy gives a 57% reduction in leprosy amongst contacts of new leprosy patients.

Finally, in the discussion, the three research questions as described in the introduction are addressed in the light of the data obtained within this thesis.