Therapeutic action of anti-leprosy drugs and some evidences of persisters in paucibacillary cases

Editorial

At present there are several drugs with a known anti-leprosy activity. In addition to sulphone, clofazimine and rifampin, other drugs exist with bactericidal activity, such as minocycline, a number of fluorquinolones and some macrolides. These drugs have their action against *Mycobacterium* leprae confirmed by experimental inoculations in the mouse footpad as indicated by Shepard and by pilot and field trials in humans[1,2]. In lepromatous leprosy it is easy to see that a drug is really effective. Bacilli and clinical lesions disappear gradually during the treatment Dead bacilli are slowly eliminated because of the low cellular immunity. There is proportionality between improvement and duration of therapy

We would think that regression of the lesions in lepromatous leprosy after beginning of treatment follows a standard pattern. Mucosal lesions disappear during the first weeks. Nasal obstruction decreases, epistaxis cease and patients are able to breath normally. The ulcerative skin lesions heal leaving scars, i.e., lepromata and infiltrates regress. For reasons such as stasis, lesions on lower limbs take longer to heal. Smaller and more recent cutaneous lesions improve while older and larger ones show some signs of regression after three to four months of treatment Clinical improvement becomes more and more evident during the following months. Infiltration of lesions changes remarkably even before the end of the first year, after that the recovery period is variable and depends on the number of viable bacilli present and on the clearance rate of the dead ones. Clinical signs of regression are not so evident during this phase. In advanced cases, the complete disappearance of bacilli and skin lesions takes four to five years[3].

In the indeterminate cases and in the tuberculoid and borderline presenting some degree of cellular immunity, we observe a completely different situation. In most cases, there is no proportional therapeutic response. The majority of indeterminate cases may regress spontaneously while the remaining cases evolve to other clinical forms, tuberculoid, borderline or lepromatous, depending on the patient's immunological status. Souza Lima and Alayon[4] periodically examined children in a leprosy settlement (Padre Bento Leprosarium) and verified that the mean time for the evolution of indeterminate leprosy was 5 years, 2 or 3 years for tuberculoid and about 5 years or more for lepromatous leprosy. In addition, 70% of the tuberculoid cases are self-limiting as well as several of the borderline cases.

Moreover, the tendency to spontaneous cure presented by such cases pose a problem to evaluate therapy, added to the poorly defined clinical and laboratory parameters. In indeterminate cases, lesions are smear-negative presented as small cutaneous patches. Their histopathological examination shows discrete lesions with rare bacilli. In addition, anaesthetic or hypoaesthetic hypochromic macules without visible abnormalities may remain quiescent for years, despite having or not being treated.

Difficulties in the evaluation criteria are also related to type 1 reactions and the action of drugs on peripheral nerve lesions.

Type 1 reactions are acute phenomena that appear during the chronic evolution of tuberculoid and borderline leprosy. In a classical type 1 reaction, chronic tuberculoid and borderline lesions become more erythematous and edematous and new Lions appear with reactional aspect. When the reactional episode ends, the patient presents a higher number of lesions; he becomes clinically "more tuberculoid" or "more borderline' Sometimes reactional lesions are practically the only manifestations of the disease. An initially anaesthetic lesion may suddenly exhibit erythema and edema encompassing the whole Dion. Papules, nodules and plaques may appear over the whole body. These sometimes self-limiting acute manifestations may occur throughout the whole leprosy spectrum. The mean duration of these episodes is 4 to 6 months. The acute phase may regress after a few days but in general a reactional episode takes several months before its lesions become flat and hypopigmented.

Only immunosuppressive drugs are able to control such acute reactional episodes, anti-mycobacterial treatment does not interfere with its evolution. Therefore, depending on the time the anti-microbial therapy is initiated, we may get the wrong impression that lesions are improving because of the treatment instead of the natural evolution of the reactional phenomenon.

Patients' files of the pre-sulphone era show the natural history of some of these acute phenomena. There are several examples of patients in whom smear positive reactional lesions disappeared spontaneously after a variable period of time[7]. The

patients remained smear negative and without lesions for years but they could suddenly present reappearance of new lesions and bacilli. A distinct behavior of the bacteria was shown in such cases and they probably did not multiply during the quiescent phase. If that indeed happened, it could be an explanation for relapses occurring during or even after the treatment today.

Therefore, except for the lepromatous patients, therapeutic evaluation for leprosy is difficult.

The anti-leprosy action of the drugs in nerves is another complicated issue. When acute phenomena occur, the effect of corticotherapy can be evaluated to some extent The specific treatment, however, demands parameters that do not exist. The disappearance of the infiltrate and bacilli that would constitute the healing process is not always traduced into improvement of neural lesions. Regression of anaestesia, vegetative and motor changes would be noticed if that was the case. The cicatricial fibrosis following the inflammatory process may cause as many damage to nerves. These cases can only be evaluated after lesions and symptoms stabilize.

Those aspects must be taken into consideration when new therapeutics schemes are proposed or medications are being evaluated.

In summary, the criteria to evaluate the effect of treatment in paucibacillary cases are limited. It seems that bacilli remain metabolically inactive during certain periods in cases presenting some degree of immunity.

In indeterminate cases treated with the MDT/PB/WHO, this behavior has been noticed. Rifampin, a highly bactericidal drug destroys 99.9% of bacilli in lepromatous leprosy cases. In indeterminate cases, with a much lower number of bacilli, a single 600 mg dose would be enough to eliminate all of them. Nevertheless, 6 doses with a month interval are prescribed and still, signs of disease activity are noticed in some cases after the end of treatment. Similar situation is observed in patients with a single lesions receiving one dose of ROM[8], despite the powerful bactericidal effect of the three associated drugs.

Finally, in order to verify the activity of a drug against leprosy it is also very important to know the time period to initiate their action of a drug and the changes it imposes in the bacilli. There is an ongoing multicenter trial sponsored by the WHO that will be concluded this year. A short regimen with rifampin plus daily ofloxacin during one month is being compared with other regimens. Rifampin would kill most of the bacteria with only one dose and ofloxacin during one month would have as good bactericidal activity as rifampin to destroy the remaining bacilli. It seems, however, that an unacceptable number of relapses have occurred after completion of the treatment.

What is happening? It is conceivable that the lag phase induced by the rapid action of rifampin would interfere with the action of ofloxacin. Many bacilli that were not initially destroyed started to multiply again and were no longer under action of the drugs.

That is why the speed a drug initiates its activity is very important. It has been described in tuberculosis that sub-populations of persister microbes multiply, when they multiply they divide only during 20 minutes. Since isoniazide bactericidal activity against *Mycobacterium tuberculosis* takes 12 hours to initiate its action and kill the bacillus', only a drug such as rifampin would be effective. The time needed to initiate the killing action of a given drug may also be an explanation for the fact that the type I reactions happened more frequently during sulphone monotherapy.

That is the reasons why the evolution of the disease, behavior of persister bacilli and activity of the drugs are relevant parameters for evaluation of treatment in paucibacillary leprosy patients. But these parameters are not always observed!

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