

# Treatment of the reactions in leprosy

Editorial

There are two types of reactions in Hansen disease (HD): the type 1 reactions that occur in patients that still have a cell mediated immunity (CMI) to *M. leprae* and the type 2 reactions or erythema nodosum leprosum that occur in patients without or with little CMI against the Hansen bacilli. The humoral immune system; antibodies and complement, is responsible for these reactions.

Frequently both reactions are accompanied by neural involvement and this is the cause of most of the deformity and disability in this disease.

In type 2 reactions, together or independent of nerve involvement, cutaneous lesions may ulcerate. Sometimes there is an involvement of the small joints and muscles of the hands (reactional hands) that cause deformities similar to rheumatoid arthritis. Acute ocular lesions, orchitis leading to gynaecomastia may occur and manifestations in other organs with a lower risk to cause disabilities. To prevent deformities and disabilities are the main reasons why the treatment of these acute phenomena is of such a great importance.

For the type 1 reactions the only really effective drugs are still the steroids. However there is need to restrict their use to cases with neuritis and when the reactions are really occurring and not as a prophylactic. Too many patients then will get a potential dangerous drug that they do not need.

When a patient present during a type-1 with erythematous plaques around the eyes or on the cheeks, and when the branch of facial nerve to the orbicular muscle of the eyelids is involved the patient will present with lagophthalmos during the reactional episode. In my opinion if he doesn't present neural involvement during these episodes, there is no reason to utilize the steroids to avoid this involvement. The same and possible with more reasons when the reactional skin lesions are located in ulnar or median nerve distribution. The same applies for other nerves.

However when severe edema in the extremities with limitation of movements occurs or the social functioning of a patient is hampered when the lesions involve the face, only then is the use of steroids justified. In the other cases, when there is no risk of nerve damage the treatment must be only symptomatic, for instance with non-steroid anti-inflammatory drugs.

NSAID's)

Thalidomide has not any beneficial effect in this kind of reactions. Naafs' refers to azothiaprine as a drug that could be used in patients that are intolerant to the steroids, but it substitutes these drugs only partially and is of little use in the early phase of treatment since it misses the quick action on the intraneural edema that steroids have.

Chin-A-Lien et al.', consider cyclosporine A as effective as steroids in the treatment of reversal reaction (type-1). Theoretically Cyclosporine A would be an ideal drug because it primarily acts suppressing CD4 Th1 helper cells. However it misses also the quick anti-edema action of the steroids. Be it as it may, the drugs cited have no proper control studies to confirm without doubt their activity in the type 1 reactions.

Type 2 reactions have a little more therapeutic options. The reactions may manifest with several grades of severity. During mild episodes only symptomatic treatment could be used. During more severe reactions thalidomide may be employed but this is forbidden for sexually active women. In the remaining cases steroids are the drugs used. Absolute indications for the steroids are those cases with severe neuritis, eye and testes involvement.

Unfortunately there are no other drugs that are really effective in the treatment of these reactional states.

Some authors are of the opinion that clofazimine could be another therapeutic option for the type 2 reactions, due to its presumed anti-inflammatory property. At the Bergen Congress' in 1973 the Therapeutic Commission states that clofazimine could be useful for treatment of Erythema nodosum leprosum in the dose of 200 to 300 mg daily, but when the anti reactional effect not is seen within 6 weeks it should be combined with thalidomide or steroids. Based on the conclusions of this Congress it can be assumed that if clofazimine has any anti-reactional activity it must very weak.

Some authors<sup>4</sup> believe also that occurrence of the type 2 reactions is lower after the introduction of MDT/WHO due the action of this rimino compound, even though it is been used in doses smaller than that recommended for the treatment of these episodes. However there are others researchers considering that the ENL increased in this period.

A great number of thalidomide analogs has been synthesized using this drug as lead structure'. Some of them are potent inhibitors of the phosphodiesterase type IV, are highly active in the inhibition of the production of TNF- $\alpha$  in humans PBMC's and in the protection of mice from the lethality induced by LPS. If these analogs will have the same activity as that of thalidomide, without its teratogenic effects, our therapeutic arsenal against the reactional state will be very much improved.

Some time ago it was found that during the type 2 reactions there was an increase in TNF- $\alpha$  and it was suggested that thalidomide would act by inhibition of the production of this cytokine in the treatment of reactions"". However there are papers that showed normal or even lowered levels of TNF- $\alpha$  during type 2 reactions and that even thalidomide's positive therapeutic effect in other conditions could be due to an increase in the levels of TNF- $\alpha$ ". It was also shown that this drug "in vitro" is not particularly a potent inhibitor of this cytokine'. Because it was fashionable to think that TNF- $\alpha$  was an important factor in the pathogenesis of ENL the search for drugs that could inhibit this factor has been great.

When pentoxifylline showed to have a high ability to decrease TNF- $\alpha$  levels"" some researchers initiated a study in leprosy. We are not aware of controlled studies with this drug in type 2 reaction'. There are only uncontrolled studies presented in letters to the "International Journal of Leprosy"<sup>7,13</sup> and Leprosy Review" editors, and a paper in the "Clinical Experimental Immunology'. So far twenty-five cases have been published, however the results are not very impressive. In one of the papers' patients were treated with pentoxifylline, thalidomide and prednisone respectively. In the group of six patients that were given thalidomide in the dose of 300 mg per day, three patients entered directly the treatment with that drug and the remaining were patients that didn't have a satisfactory response to the treatment with pentoxifylline. 5/6 patients showed complete clinical remission by the 14th day.

Naafs' also has not seen any particular effect of pentoxifylline in the treatment of ENL. On the other hand a recent paper by Welsh et al.' showed a good result in 4 patients with type-2 reactions, with clofazimine (100 mg every 8 hours) plus pentoxifylline (400 mg every 8 hours). The authors referred already that when they used the drugs alone that the results were not good, but when they combined both drugs the result was rapid and the patients became in 7 to 10 days symptomless.

Another drug able to reduce the TNF- $\alpha$  is zafirlukast that was used to treat reactions in leprosy by Vides et al". These authors refer Calhoun et al., who

showed this drug to be also an inhibitor of the leucotriene receptor and to reduce the concentrations of TNF- $\alpha$  and superoxide anion in the bronchio-alveolar washing fluid in an asthmatic patient elicited by antigen.

The authors treated type 1 reactions and type 2 reactions with good results. It was not convincing to see two kinds of reactional episodes mediated by different immunophenomena to have a very good response to a therapeutic. Moreover it was not a controlled study.

Recently Naafs' reviewed drugs that were used at some time in the treatment of type 2 reactions. He wrote that antimonials could interfere with complement activation and could be used in type 2 reactions in combination with prostaglandin inhibitors. Chlorpromazine also could be useful and had been shown to inhibit complement-mediated reactions in rabbits and inhibited tissue damage. Prometazine would be another drug that is able to improve ENL. It inhibits the complement cascade and interferes with mediators liberated by mastocytes, alleviating the symptoms. When ENL does not present with evident deterioration of neural function, it is possible to treat it with a combination of non-steroid anti-inflammatory drugs and antimalarials such as chloroquine and hydroxychloroquine. Antimalarial drugs stabilize lysosomal membranes, thus avoiding tissue destruction and inhibiting complement activation by the antigen-antibody complex.

Other drugs that have been considered in the treatment of ENL are colchicine that inhibits vascular damage in experimental Arthus-type reactions, hindering neutrophil chemotaxis, and cyclosporine-A that has been claimed useful in severe ENL<sup>17,18</sup>

The good results attributed to these drugs however are more related to the experience of the researchers than to well designed clinical studies. It is very difficult to compare drugs as thalidomide and steroids that nearly always show their activity within a few hours with other drugs that are claimed to be active and of which the beneficial effects only may appear after several days or even weeks. We should therefore not forget that in the majority of cases ENL is a self-limiting phenomenon, it takes usually between 15 to 20 days to disappear spontaneously.

Actually there are at present no drugs that can replace thalidomide or steroids in the treatment of leprosy reactions. For that reason one should be careful with the recommendations of drugs without elaborated well-controlled studies and not create false expectations. However that is unfortunately what is happening.!

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