Letter to the Editor

CHRONIC RECURRENT ENL, STEROID DEPENDENT: LONG-TERM TREATMENT WITH HIGH DOSE CLOFAZIMINE

Recent months have seen a surge of interest in the treatment of severe, chronic recurrent erythema nodosum leprosum (ENL). This is a serious problem, which for unknown reasons in the past few years has not received the attention it deserves. It is certainly not uncommon when visiting leprosy clinics to find such patients. They are often in dire need of effective and safe treatment, since there is a great danger that these patients with chronic recurrent ENL become steroid dependent, due to the limitations and dangers of steroid treatment and the limitations or non-availability of other effective drugs like thalidomide. This may occur even when the underlying factors that have been recognized to contribute to the establishment of chronic ENL have been adequately addressed (e.g. chronic infections, anaemia, stress). It is not often realized that adjuvant drugs such as chlorpromazine and a high dose of clofazimine may reduce the need for steroids.

The reasons for steroid dependency are not clear, but at least in some cases it can be prevented by some prudence when prescribing steroids:

- Reserve steroids only for severe ENL reaction (e.g. neuritis with increasing neuropathy, iridocyclitis, ulcerating skin lesions with fever or other organ involvement; arthritis, lymphadenitis, orchitis, hepatitis, not reacting to standard treatment).
- Start with high dose of steroids (1–2 mg/kg body weight). Reduce rapidly (pulse therapy) with intended maximum treatment duration of not more than 3–4 weeks (the natural duration of an ENL attack). Try to prevent a maintenance dose. If there is a recurrent attack during the tapering off period, the current dosage should be doubled. When efficacy is observed, the dosage should be tapered off again. The advice of WHO to continue steroids for at least 3 months (e.g. PREDNIPAK), similarly to the treatment of reversal reactions, is asking for problems, since ENL is an episodic occurrence. Moreover the advised initial dose is too low for most patients.
- Based on experience from the past, concurrent with steroids, a course of clofazimine should be prescribed. In many countries (e.g. Indonesia, Brazil), national guidelines advise the prescription of clofazimine particularly in cases of recurrent severe ENL. This is often not done.
- Prevent self-prescription of steroids by patients or inexperienced staff.

Thalidomide has proven to be a very effective drug in cases of severe ENL, however, it cannot completely replace steroids. Signs and symptoms may resolve even more rapidly than with steroids, but in case of acute nerve damage and/or iridocyclitis, a high initial dose of steroids may be needed. The problem with thalidomide is that it cannot be
prescribed to women of child-bearing age who do not have 100% safe contraception.\textsuperscript{20–29} Furthermore, in many countries thalidomide is not available.\textsuperscript{5} Newer drugs such as cyclosporine are being put to clinical trials, but are expensive and probably not as effective\textsuperscript{10,13,30} and not always available. Pentoxifylline, advocated as an alternative to thalidomide, has showed some effect,\textsuperscript{31–33} but some clinicians are not particularly impressed.\textsuperscript{10,13,34}

Clofazimine will not relieve acute symptoms.\textsuperscript{16–19} It is not a very effective anti-ENL drug and moreover is slow-acting.\textsuperscript{16–19,35,36} In drug regimes, including WHO-MDT, fewer ENL reactions are recorded.\textsuperscript{37–40} This suggests, therefore, that clofazimine could probably be used in the successful control of chronic recurrent ENL. In the Netherlands, among those who took dapsone monotherapy, 28% developed moderate to severe ENL. Over a period of 2 years from those on WHO-MDT, 14% developed ENL. After MDT, another 5% also developed ENL.\textsuperscript{39} Clofazimine is widely available and only causes serious side effects (abdominal problems, e.g. bowel obstruction, gastrointestinal bleeding, splenic infarction and hepatitis, dyspigmentation and dry ichthyotic skin\textsuperscript{41–46}) in a few patients.

Patients who develop several bouts of ENL over a short period of time should be prescribed a high dose of clofazimine with a starting dose of 300 mg daily for at least 2 months,\textsuperscript{4,18} together with drugs to relieve the acute symptoms (e.g. steroids). When a patient continues having ENL reactions, 200–300 mg daily should be maintained for longer periods, and if the patient is on steroids, the steroids should be reduced slowly (to zero) under the protective umbrella of clofazimine. When thalidomide is available and can be prescribed, it could be used or added to replace the steroids.\textsuperscript{26} If no new ENL reactions appear and the patient is no longer on steroids, clofazimine can slowly be reduced to 200 mg daily for 2 months, to 100 mg daily for 2 months, etc. Clofazimine can be given in high doses over long periods to wean dependent patients from steroids.

This is clearly not a magical solution,\textsuperscript{35,36,48} and it can sometimes take a year or even more before the patient will be steroid free. However, this is far preferable to having steroid-dependent patients to look after. It must be kept in mind that though most authors feel the improvement is a clofazimine effect,\textsuperscript{16–19,26} some authors are of the opinion that it may be just a time effect, the disease following its natural course.\textsuperscript{3}

It is our opinion that careful management of an ENL reaction may in many cases prevent steroid dependency, and that in the management there is a place for clofazimine. We would recommend its use and it should be made available also outside the blister packs.

To find a definite answer to the question of the place of (long-term, high-dose) clofazimine in the prevention and treatment of chronic recurrent, steroid-dependent ENL, a controlled clinical trial is warranted.

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References

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