Research letter

Oral erythromycin therapy in epidermolysis bullosa simplex generalized severe

DOI: 10.1111/bjd.13672

Dear Editor, Hereditary epidermolysis bullosa simplex generalized severe (EBS-gen-sev; formerly known as Dowling–Meara EBS) is the most severe form of EBS,[1] and at present, no effective therapy exists. The use of tetracycline to treat EBS is controversial,[2,3] and is contraindicated in childhood, when the disease can be most severe. Macrolides are used to treat various inflammatory skin diseases[4] and are suitable for treating children. In this open-label preliminary study without controls, we evaluated whether oral erythromycin could be an effective and well-tolerated treatment in children with EBS-gen-sev.

Patients of both sexes, aged 1–8 years who had EBS-gen-sev with at least two new blisters per day were eligible for the study. The treatment consisted of oral soluble erythromycin for 3 months. A weight-based dosage was calculated for the children (< 10 kg, 250 mg per day; 10–15 kg, 500 mg per day; 15–25 kg, 750 mg per day; 25–35 kg, 1000 mg per day). Therapeutic success was defined as a decrease of at least 20% in the mean number of new blisters per day calculated over the course of 1 week at the end of treatment.

At baseline, after 1 month and 3 months of treatment, the patients were seen for body examination, questionnaire, photographs, blood tests and bacteriological swabs. Itch severity and skin fragility were evaluated by parents on a visual analogue scale. At 5 months, we asked all parents for their opinion regarding the tolerability and efficacy of the treatment.

Six patients (rather than eight as initially planned), with a mean age of 4·6 years, were selected for the study in the summer. Patient 5 took steroids during month 2 and antibiotics and steroids during month 4 for noncutaneous infectious disease. Patient 6 took antibiotics during month 1. Only patients 1–5 completed the study. Therapeutic success was achieved for patients 2, 3 and 5, with a mean decrease in the number of new blisters per day of 41% (Fig. 1). Itch severity and skin fragility scores did not show that oral erythromycin had any effect on these symptoms.

Parents evaluated the efficacy of treatment as 'good' or 'very good' in two cases and 'bad' in three cases. Interestingly, one patient who achieved clinical success did not consider the treatment to be effective, even though the number of new blisters per day decreased by 24% at month 3 compared with baseline. The analysis of intermediate results at month 1 showed an increase in the number of new blisters per day for all patients.

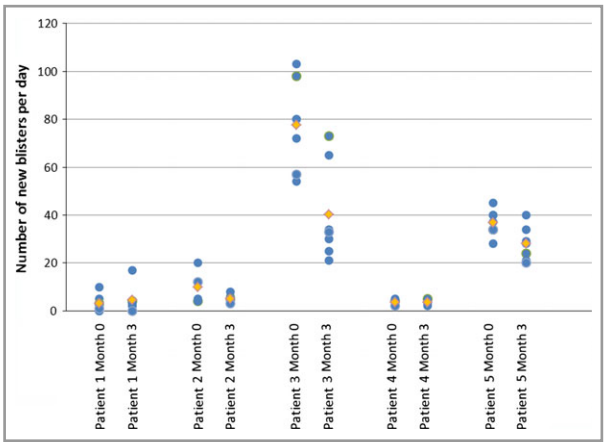

Fig 1. The evolution of the number of new blisters per day for each patient at baseline and after 3 months of treatment with oral erythromycin.

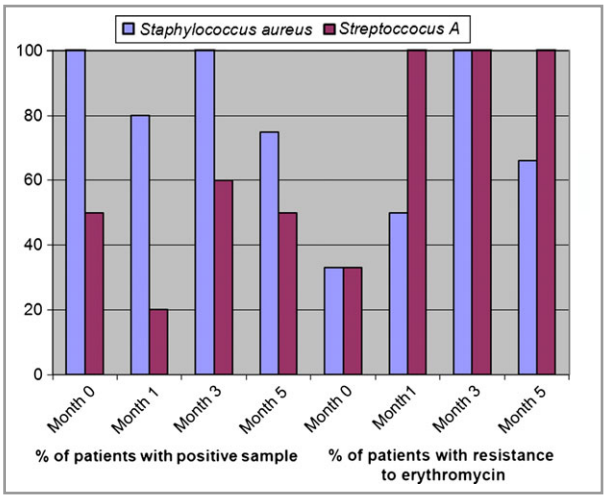

Fig 2. Evolution of skin colonization by *Staphylococcus aureus* and *Streptococcus A* during the study and its resistance to erythromycin.

Five adverse events, which were not related to erythromycin, were reported during the study. The tolerability of the treatment was evaluated as 'good' by five patients and 'poor' by patient 6, who did not complete the study.

At baseline, all six patients had skin colonization by *Staphylococcus aureus* and three had skin colonization by *Streptococcus A* (Fig. 2). Resistance to erythromycin was seen in only two of the patients with skin colonization by *S. aureus* and one of the

three patients with skin colonization by *Streptococcus A*. At month 3, the percentage of skin colonization was similar to that seen at baseline for *S. aureus* but slightly more pronounced for *Streptococcus A* (three of five patients). However, all of these five patients had become resistant to erythromycin. Two months after the end of the treatment, only one patient had *S. aureus* that was sensitive to erythromycin. A comparison of blisters vs. nasal colonization during the study showed similar results.

Despite the low number of patients enrolled and the absence of controls, there are insights to be gained from this study. Firstly, the three patients who achieved therapeutic success were those who initially had the higher number of blisters.

Secondly, long-term treatment with oral erythromycin is well tolerated in children, even in those who are very young. These findings were already suggested by reports on childhood rosacea and infantile acne,[4–6] but to our knowledge, no systematic evaluation of clinical and biological side-effects was carried out in these studies.

Thirdly, long-term treatment with oral erythromycin induced bacterial resistance in all patients. This is of interest because it suggests that erythromycin acts through an anti-inflammatory mechanism rather than through antimicrobial activity. The absence of any clinical improvement after 1 month of treatment reinforces this idea, and it is also supported by the known immunomodulatory properties of macrolides and recent publications about the role of inflammatory mechanisms in EBS-gen-sev.[7,8] Thus, our results are in agreement with those obtained by Weiner *et al.*[2] concerning the benefits of using tetracycline to treat patients with EBS. On the other hand, the role of bacterial colonization of the skin is not elucidated. Three of the patients in our study continued to have skin colonization with *S. aureus* that was sensitive to erythromycin 1·5 years after the end of the study, suggesting that this resistance is transient.

Fourthly, other researchers have found that it is difficult to recruit patients with EBS-gen-sev for national trials.[2,9] Finally, despite achieving therapeutic success, one patient judged the treatment to be ineffective. This underscores the need to choose end points that are clinically relevant for the patient. These findings are of importance for further studies that address the pharmacological treatment of EBS-gen-sev.

In conclusion, this study suggests that long-term oral erythromycin might be a safe alternative for some patients with EBS-gen-sev. An international, double-blind, randomized vs. placebo study is necessary to investigate this further.

Acknowledgments

Logistical help has been provided by the Clinical Research Centre of Nice. DEBRA France helped us to inform patients.

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Funding sources: This work has been funded by Expanscience Laboratory and the French Society of Dermatology.

Conflicts of interest: none declared.