

CLOFAZIMINE-ENHANCED PHAGOCYTOSIS IN PUSTULOSIS PALMARIS ET PLANTARIS

Lars Molin

From the Department of Dermatology, Karolinska sjukhuset, Stockholm, Sweden

Abstract: The phagocytic ability of neutrophil leucocytes was found to be impaired in patients suffering from pustulosis palmaris et plantaris (PPP). This ability was studied with the aid of the yeast particle method. In 78% of 27 patients whose PPP was in a static phase, the phagocytic function was enhanced, while the PPP abated concomitantly and the pustules disappeared. Impaired phagocytosis and the beneficial effect of clofazimine signify the pathogenic importance of defective neutrophils in PPP.

Key words: Pustulosis palmaris et plantaris; Phagocytosis; Phagocytosis enhancement; Clofazimine; Neutrophil leucocytes

A defect in the phagocytic ability of neutrophilic leucocytes in vitro has previously been described in pustulosis palmaris et plantaris (PPP) as well as in other dermatoses (6, 7). Recently, Brandt demonstrated the possibility of enhancing the phagocytic activity with the aid of clofazimine (2).

The aim of the present investigation was to analyse the effect of clofazimine on phagocytosis in relation to the clinical activity of PPP.

MATERIAL AND METHOD

The investigation covered 27 patients, 8 males and 19 females. The patients had an age range from 27 to 63 (median 45) years. All had suffered from PPP for more than 3 years. During the last year, at least, the activity of the disease had been stationary, i.e. without either spontaneous or therapeutically induced remission. In 8 of the patients there were more or less stationary psoriatic nummular or plaque lesions of minimal extent (less than 5% of body surface). In the remaining 19 cases no features characteristic of psoriasis were found. Patients having other diseases such as chronic infections, polyarthritis, hematological, renal or liver diseases were not eligible for inclusion in the series.

Clofazimine (Lamprene®, Ciba-Geigy A. G., Basle, Switzerland) was administered perorally in capsules, each containing 100 mg. The initial dosage, maintained for the first months was 400 mg per day, divided in two doses. This dosage was subsequently reduced to 200-300 mg per day.

Local treatment was unchanged during the first months of the clofazimine therapy but was later considered unnecessary in many cases.

In order to determine the phagocytic activity, the ability of the neutrophils to ingest heat-killed yeast cells in vitro was investigated. The method has been described previously (1, 7). A phagocytic index (PI) was calculated, giving the mean number of phagocytised particles per neutrophil.

The PPP activity was estimated by the number of pustules on the soles and palms.

The clinical effect was recorded in a four-graded scale: + + + indicated remaining erythema or slight keratosis but no vesicles or pustules; + + indicated isolated pustules, on the soles and palms totalling less than ten; + indicated a decreased number of pustules but usually totalling more than ten on the soles and palms; 0 indicated no or uncertain effect.

The patients were examined and the PI was determined prior to the clofazimine therapy and once a month during the first 3-4 months of the therapy; later on, at longer intervals. All the patients were thus observed for more than one year.

As controls in the determination of phagocytosis, 24 blood donors were used.

RESULTS

In the 27 patients with PPP, considered as a group, the phagocytic activity (PI range 2.40-3.40, mean $\pm$ S.D. 2.84 ± 0.31) was highly significantly lower than in the controls (PI range 2.96-3.40, mean $\pm$ S.D. 3.16 ± 0.16) ($p < 0.001$).

In Fig. 1 the individual PI values prior the clofazimine therapy are indicated. During the therapy, PI increased significantly within 1 month in 17 of the patients. The figure also gives the percentage increase in the PI after 6 months of therapy. There is an obvious relationship between the initial PI prior to therapy, and the increase in PI during therapy. The lower the initial PI value was the higher was the increase of the PI value.

After 6 months, the therapeutical effect was considered very good in 21 of the 27 patients. There was

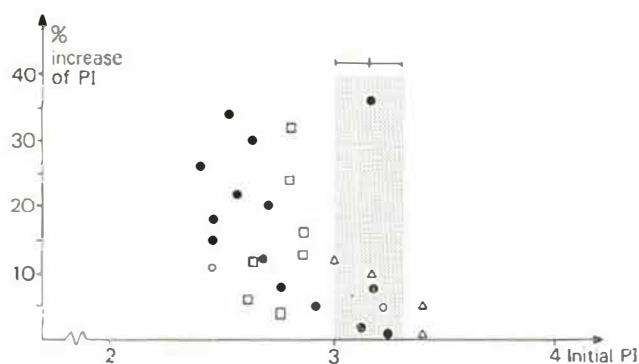


Fig. 1. Phagocytic index (PI) prior and after 6 months of clofazimine therapy in relation to the clinical effect. For grading of clinical effect, ● = + + + +, □ = + + +, △ = + +, ○ = +; see Methods. The PI in blood donor controls (mean $\pm$ standard deviation) is indicated.

remaining erythema and slight keratosis and in 7 of these 21, sometimes isolated pustules, though never more than ten together on the soles and palms. In 4 cases the PPP activity was somewhat decreased, though with episodes of more than ten pustules, and in 2 cases the therapy had no effect, or only to a very uncertain extent.

The diminished activity of the disease could usually be demonstrated within 1 month, but full clinical effect was not achieved until after 2–3 months. In 5 cases a very good clinical result after 1–3 months was followed by again increased activity of the disease in spite of continuous therapy. In 22 cases the obtained remission remained during the follow-up period. Fourteen of them completed the clofazimine therapy after 6–10 months without relapse during the subsequent 4–6 months follow-up.

In Fig. 1 the clinical effect is related to the initial PI and the increase in PI after 6 months of clofazimine therapy. In principle, the best clinical effects were found in cases with a low initial PI and a large increase in the PI during treatment.

No difference was found between males and females concerning the effect of clofazimine therapy, either on the PI or on the clinical activity of the disease. Nor was there any difference between patients with psoriasis or without.

DISCUSSION

Clofazimine is a synthesized phenazine derivate. It is active against mycobacteria, in particular *M. leprae*, but inactive against other types of microbes (8). Phenazine derivatives are redox agents, and an

enhancing effect of clofazimine on the oxygen uptake of neutrophils has recently been demonstrated in vitro (3). Thus, reactions involved in the phagocytic mechanism seem to be stimulated or facilitated by clofazimine.

The enhancement of phagocytosis by clofazimine is clearly shown in the present investigation. The mode of action of the drug in this respect is, however, still not known (2).

There is no doubt about the diminished activity of PPP during clofazimine therapy, when considering the clinical features of the disease in patients prior to treatment, as well as the clinical pattern generally found in PPP (4).

In PPP there is no explanation for the local accumulation of leucocytes. The recently demonstrated deposition of immunoglobulins and complement fraction of C3 in PPP, as well as in generalized pustular psoriasis (5), implies a hypothetical binding to the epidermal–dermal junction area of complement fractions which may act chemotactically for neutrophils. A decreased phagocytic function of the neutrophils has been suggested to be of pathogenetic importance in PPP (7). This idea is supported by the clear relationship between the increased phagocytosis and the clinical improvement shown in the present investigation.

The nosologic position of PPP is, however, far from unequivocal. The fact that PPP in some of the patients (22%) was virtually uninfluenced by the phagocytic enhancing therapy may indicate another pathogenetic mechanism in these cases. Thus, it may be hypothetically possible to use the clofazimine enhancing effect on the polymorphonuclear phagocytosis in order to distinguish between different types of PPP.

ACKNOWLEDGEMENTS

This investigation was supported by grants from the Edvard Welander Foundation and Hässle-Ciba-Geigy AB, Mölndal, Sweden.

REFERENCES

1. Brandt, L.: Studies on the phagocytic activity of neutrophilic leucocytes. *Scand J Haematol, Suppl.* 2, 1967.
2. — Enhancing effect of clofazimine (B 663) on the phagocytosis of neutrophilic leucocytes *in vitro*. *Scand J Haematol.* 8: 265, 1971.
3. Cline, M. J.: Drug potentiation of macrophage function. *Infect Immunol* 2: 601, 1970.
4. Enfors, W. & Molin, L.: Pustulosis palmaris et plantaris. A follow-up study of a ten-year material. *Acta Dermatovener (Stockholm)* 51: 289, 1971.
5. Hushy, G., Rajka, G. & Eeg Larsen, T.: Immunofluorescence studies in pustulosis palmo-plantaris. *Acta Dermatovener (Stockholm)* 53: 123, 1973.
6. Michaëlsson, G.: Decreased phagocytic capacity of the neutrophil leucocytes in patients with atopic dermatitis. *Acta Dermatovener (Stockholm)* 53: 279, 1973.
7. Molin, L. & Rajka, G.: Phagocytic activity of neutrophil leucocytes in pustulosis palmo-plantaris, chronic discoid lupus erythematosus and erysipelas. *Acta Dermatovener (Stockholm)* 51: 138, 1971.
8. Vischer, W. A.: The experimental properties of G 30320 (B 663)—a new anti-leprotic agent. *Leprosy Rev* 40: 107, 1969.

Received June 27, 1974

L. Molin, M.D.
Department of Dermatology
Regionsjukhuset
S-581 85 Linköping
Sweden