Acta Dermatovener (Stockholm) 50: 445–450, 1970

# PSORIASIS TREATED WITH BUSULFAN

Halvor Möller and Jan Waldenström

*From the Departments of Dermatology and Internal Medicine, University of Lund, Malmö General Hospital, Malmö, Sweden*

*Abstract.* Because of repeated remissions of psoriasis in a patient treated with busulfan (Myleran®) for chronic myeloic leukemia a double-blind cross-over study with this drug was conducted in 9 patients with psoriasis. Five patients were ameliorated and 4 uninfluenced by the drug. There was a slight depression of leucocytes and thrombocytes but no other side-effects. Busulfan is a possible alternative to methotrexate in severe psoriasis.

Cytostatic treatment with methylaminopterin (methotrexate®) is now an established routine in resistant cases of psoriasis. Nevertheless, there is still a need for alternatives in cases where the result is poor, or when optimal doses cannot be reached because of toxic side-effects. Looking for another cytostatic drug for psoriasis, we were impressed by the spectacular and repeated remissions induced in this disease in a patient treated for chronic myeloic leukemia with busulfan. Stimulated by this experience, we started a double-blind trial with busulfan in a small series of patients with psoriasis.

## MATERIAL AND METHODS

The material consisted initially of 10 patients with psoriasis (Table I). There were 7 males and 3 females with the age range of 41–63 years. The skin disease was usually extensive and of long duration. One of the male patients and 2 of the females also had psoriatic arthropathy. Most patients were considered therapeutic problems and had earlier received methotrexate treatment.

The patients' regular topical therapy was continued during the study. A careful history was noted before starting the trial and skin findings were assessed clinically. Close-up colour photographs were taken of some representative diseased areas.

Coded tablets of busulfan (Myleran®) were given in a daily oral dose of 4 mg for 2 months. This treatment period was followed—or preceded—by 2 months with placebo. Thus, the trial was conducted as a double-blind cross-over study. Patients were clinically examined, as well as photographed at identical skin areas (by H. M.) when changing tablets after 2 months and when finishing the course after another 2 months. During the entire 4 month study a white blood and platelet count was checked twice a week, this being recorded independently by J. W.

To evaluate the influence of busulfan on psoriatic activity, data were compiled from the subjective impression of the patients and the clinical signs. To these findings were added the changes noted in the colour photographs.

For statistical analysis,[1] the clinical evaluation was based on the disease state in the second 2 month period compared with the first period regardless of given treatment. The sign test was used on the results in 9 patients. (One male patient was dropped from the study after 1 month because of exacerbating psoriasis; he was later found to be on placebo at that time.)

## RESULTS

When breaking the code it was found that 5 patients had taken busulfan during period I and the other 4, placebo (Table II). Period II was considered best in 3 patients (on drug) and worse in 2 patients (on placebo). In the other 4 patients period II was neither better nor worse than period I. Thus, the skin condition was ameliorated by busulfan in 5 patients, uninfluenced in 4, and impaired in none (Figs. 1–2). The effect was significant at the 5 % level.

The effect of busulfan was not correlated to a certain age or sex, to a certain type of psoriasis, or even to a previous effect of methotrexate (Table I).

## DISCUSSION

Besides aminopterin and methotrexate, cytostatic drugs of all classes have been evaluated in "in-

[1] The analysis was performed by Peter Vorwerk, Ph.D., statistical adviser of the Swedish Medical Research Council.

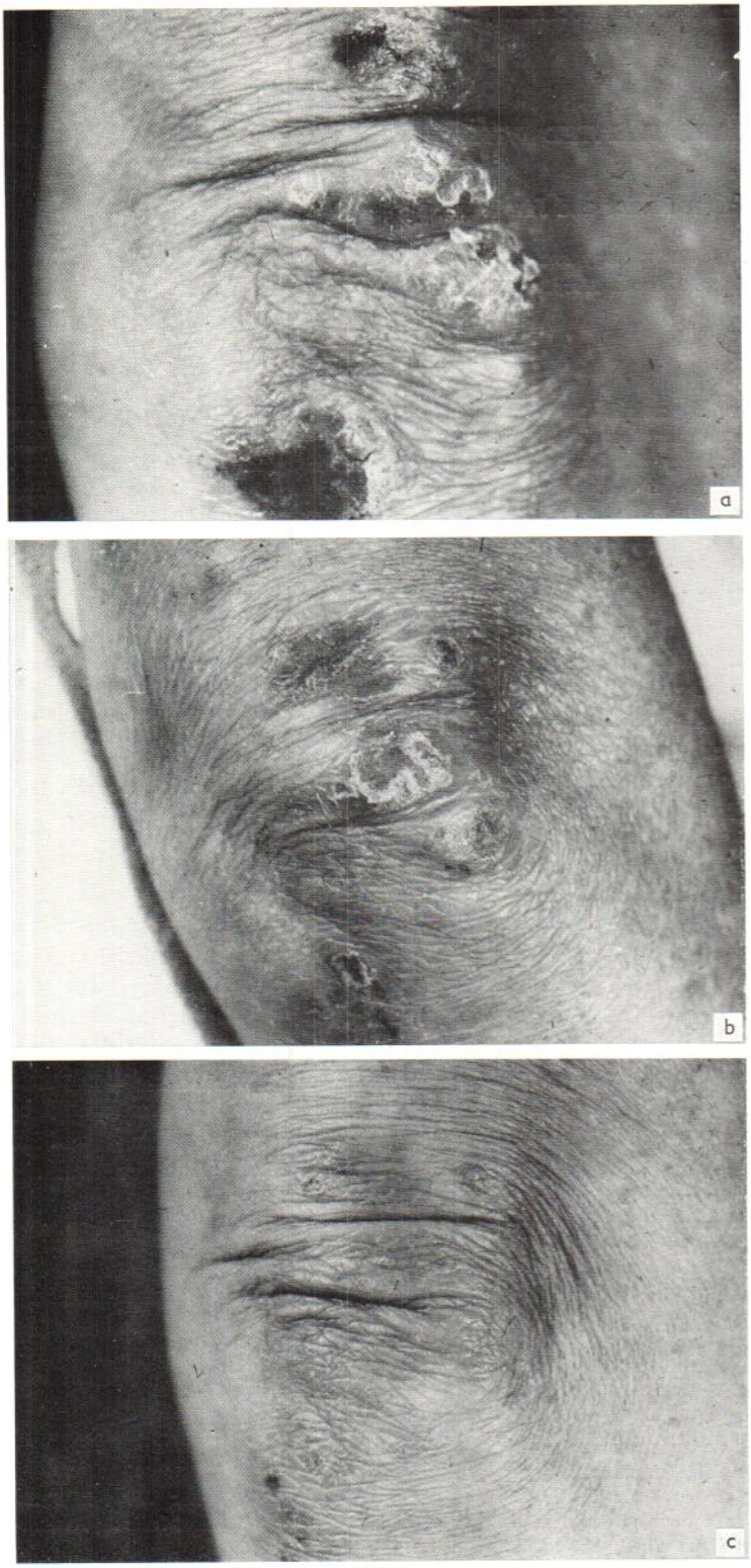


*Fig. 1.* (*a*) Elbow of patient C at start. (*b*) After 2 months with placebo. (*c*) After 2 months with busulfan.

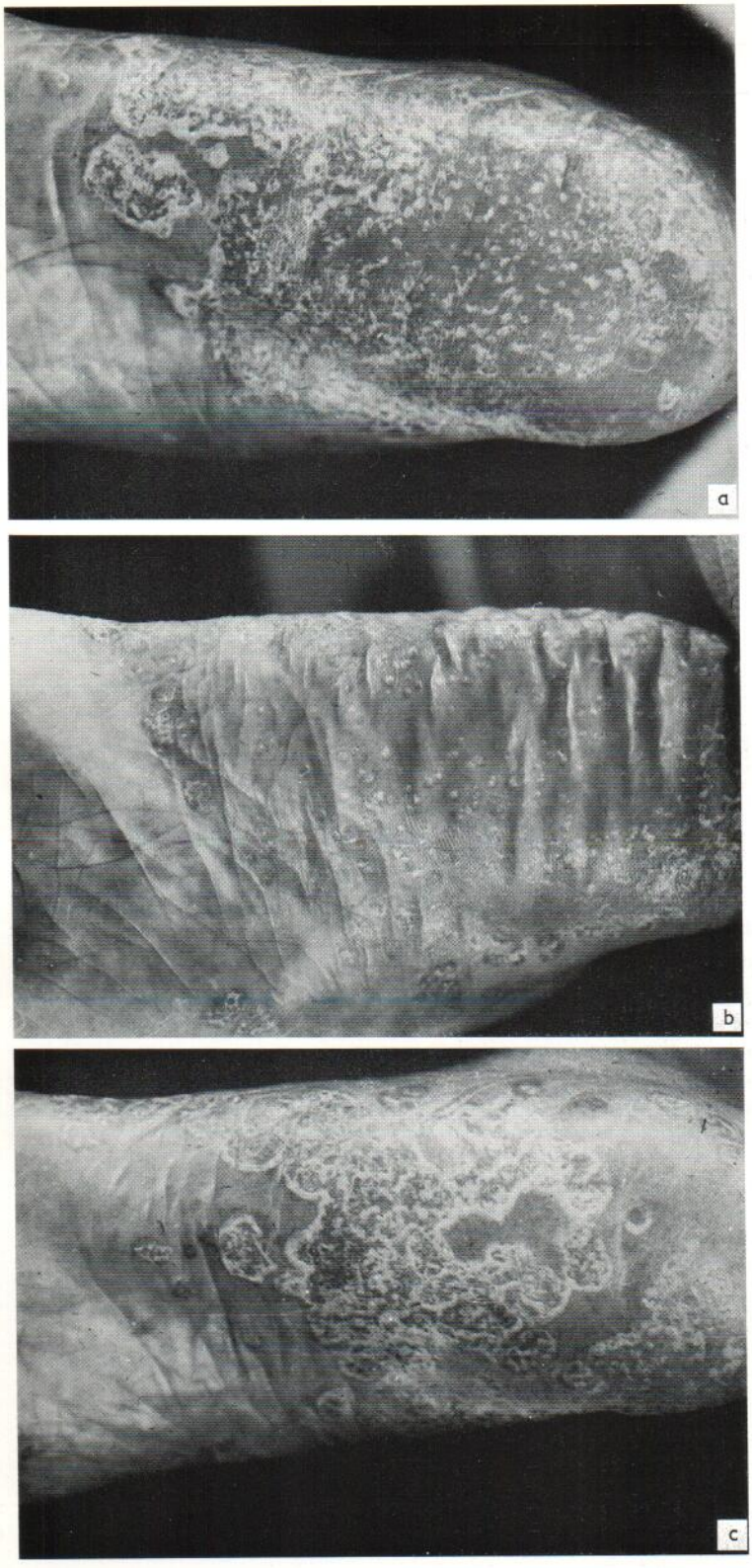


*Fig. 2.* (*a*) Sole of patient D at start. (*b*) After 2 months with busulfan. (*c*) After 2 months with placebo.

Table I. *Busulfan-treated patients with psoriasis*

| Patients... | A | B | C | D | E | F | G | H | J |
|---|---|---|---|---|---|---|---|---|---|
| Age when studied | 63 | 43 | 50 | 50 | 41 | 50 | 60 | 53 | 60 |
| Age at debut | 31 | 28 | 38 | 47 | 24 | 45 | 40 | 38 | 17 |
| Sex | ♂ | ♂ | ♀ | ♀ | ♂ | ♂ | ♂ | ♂ | ♀ |
| Heredity | − | − | − | − | + | − | + | + | + |
| Skin area | Generalized | Generalized | Extremities Scalp | Extremities Scalp | Extremities | Extremities Back, scalp | Generalized | Extremities Scalp | Extremities |
| Lesions | Nodular infiltrates | Nodular infiltrates | Discoid plaques | Discoid infiltrates | Discoid plaques | Discoid plaques | Diffuse infiltration | Discoid plaques | Macules-papules |
| Desquamation | Little | Little | Moderate | Moderate | Moderate | Moderate | Moderate | Moderate | Moderate |
| Itching | Moderate or strong | Strong | Moderate | None | Moderate | None | Slight | None | Moderate |
| Extracutaneous | — | Nails | Joints Nails | Joints Nails | Nails | — | Joints Nails | — | — |
| Course | Continuous | Continuous | Periodical | Continuous | Periodical | Continuous | Periodical | Periodical | Periodical |
| Effect of methotrexate | Unknown | None | Good | Unknown | Unknown | Unknown | Good | Unknown | Good |
| Benefit from busulfan | + | − | + | + | + | − | + | − | − |

tractable" cases of psoriasis; these trials are listed in Table III. The benefit recorded in the table is based on the results as interpreted by the present authors. No complete cures have been claimed, mainly because of the natural recurrence tendency of the disease, but also because of small margins to toxic side-effects of the drugs. On the other hand, moderate-to-considerable amelioration has been obtained with most compounds.

Not surprisingly, most trials seem to have been performed and most successes registered with the antimetabolites. This group also contains the dominant drug in the field, methotrexate. The accelerated nucleic acid synthesis pertaining to the psoriatic lesions makes these tissues particularly sensitive to the competitive intrusion of purine and pyrimidine analogues, as well as folic acid antagonists. Hereby the *de novo* synthesis of purine and pyrimidine bases is inhibited, or their incorporation in DNA disturbed. As a consequence, the psoriatic plaque, lacking adequate proteinic building-blocks, is thinning out and clinically normalizing. By definition, hyperplasia proceeds as soon as the antimetabolic interference is withheld and no rebound phenomenon may then be expected to occur.

Alkylating agents have been tested in psoriasis with varying success. Nitrogen mustard was used

Table II. *Order of medication, evaluation of last treatment period, and busulfan effect in 9 patients with psoriasis*

| Patient | Period I | Period II | Evaluation of period II | Benefit from busulfan |
|---|---|---|---|---|
| A | Placebo | Drug | Best | + |
| B | Drug | Placebo | No influence | − |
| C | Placebo | Drug | Best | + |
| D | Drug | Placebo | Worse | + |
| E | Drug | Placebo | Worse | + |
| F | Drug | Placebo | No influence | − |
| G | Placebo | Drug | Best | + |
| H | Placebo | Drug | No influence | − |
| J | Drug | Placebo | No influence | − |

Table III. *Cytostatics given for psoriasis (aminopterin and methotrexate not listed)*

| | Reference | Benefit |
|---|---|---|
| *Alkylating agents* | | |
| Nitrogen mustard | 5, 12 | + (+) |
| Busulfan (Myleran®) | Present study | (+) |
| Cyclophosphamide (Sendoxan®) | 3, 5 | + (+) |
| *Antimetabolites* | | |
| Purine bases: | | |
| 6-Mercaptopurine | 4, 5, 6, 9 | (+) − + − |
| Azathioprin (Imurel®) | 1, 3 | + + |
| Buthiopurin (Cytogran®) | 8 | + |
| Pyrimidine bases: | | |
| Daraprim® | 9 | − |
| 5-Fluorourazil | 11 | (+) |
| Triazetyl-azauridine | 10 | + |
| *Plant alkaloid* | | |
| Colchicine | 7, 11 | (+) − |
| *Antibiotics* | | |
| Actinomycin C | 3 | (+) |
| Actinomycin D | 11 | (+) |

early, even topically (12), but abandoned because of its toxicity. Cyclophosphamide in one report (3) was helpful in 80% of patients within 20 days. No other alkylators seem to have been given to psoriatic patients although, theoretically, such trials appear warranted. These drugs all contain at least two alkylating groups, usually 2-chlorethyl groups. With their bifunctional structure, cross-linking occurs between DNA chains, the reaction between guanin bases probably being the most important. Following alkylation, DNA is broken down.

The present study using busulfan as alkylating agent is the first psoriatic material published with that drug. Five psoriatics of the 9 tested were objectively ameliorated by busulfan, this being assessed with clinical examination and colour photography. The skin disease was stationary in the other 4 patients, none deteriorating during busulfan treatment. The remission was seen as a thinning-out and fading of plaques, and a decrease in desquamation. No one was completely cured. The patients reported a diminishing itching, a decrease in desquamation, and less need for topical corticosteroids. The patients' enthusiasm, however, tended to comprise both drug and placebo periods which stresses the absolute need for a double-blind study in this and similar diseases with a fluctuating and capricious course. It is noteworthy that not one of the studies referred to in Table III was designed as such. Another disturbing factor when evaluating any systemic drug in psoriasis, the influence of simultaneously given topical therapy, may be disregarded in a double-blind study.

Busulfan, as other alkylating compounds, acts upon rapidly dividing cells, such as those of bone marrow, the gastrointestinal tract, and hair roots (2). The most frequent serious effect is exerted on the marrow granulocytes and platelets. Late toxicity includes pulmonary fibrosis, and an Addisonian syndrome of hyperpigmentation, weakness, anorexia and weight loss. No subjective side-effects were noted in our patients during their 2 month course of busulfan in regular leukemia dosage, nor with placebo. The mean level of white blood and platelet counts during the busulfan periods was somewhat depressed, an effect usually seen after 3–4 weeks of therapy. Subnormal blood values were, however, never observed; this is underlined since patients with a normal bone marrow are supposed to be less resistant to busulfan than those with leukemia (2). The same degree of hematological influence of busulfan was registered in the 5 patients benefitting from the drug as in the other 4 patients.

It is concluded that busulfan, mainly because of its lower toxicity, should be considered a possible alternative to methotrexate in extensive and disabling cases of psoriasis.

## ACKNOWLEDGEMENT

We gratefully acknowledge the supply and coding of Myleran® and placebo from the Wellcome Foundation Ltd., London, England.

## REFERENCES

1. Becke, R. F. A.: The nature and treatment of psoriasis. Med J Aust *1:* 1196, 1968.
2. Boesen, E. & Davis, W.: Cytotoxic Drugs in the Treatment of Cancer. Edward Arnold (Publ.) Ltd., London, 1969.
3. Finzi, A. F.: Uso di diversi farmaci citostatici nella cura della psoriasi. Minerva Derm *44:* 47, 1969.
4. Fredriksson, T., Lodin, A. & Modée, J.: Psoriasis treated with mercaptopurine (purinethol). Acta Dermatovener (Stockholm) *47:* 196, 1967.
5. Higgins, L. C., Jr & Thompson, J. G.: Psoriasis with arthritis: chemotherapy with cyclophosphamide, nitro-

gen mustard and 6-mercaptopurine. Southern Med J *59:* 1191, 1966.
6. Kravetz, R. E. & Balsam, T.: Treatment of psoriasis with mercaptopurine. Arch Derm *84:* 597, 1961.
7. Malkinson, F. D. & Lynfield, Y. L.: Colchicine alopecia. J Invest Derm *33:* 371, 1959.
8. Novotný, F.: Léčení psoriázy Cytogranem Spofa. Čs derm *43:* 385, 1968.
9. Rees, R. B. & Bennett, J. H.: Further observations on aminopterin for psoriasis. J Invest Derm *32:* 61, 1959.
10. Turner, R. W. & Calabresi, P.: The effect of triacetyl azauridine on psoriasis. J Invest Derm *43:* 551, 1964.
11. Van Scott, E. J. & Reinertson, R. P.: Morphologic and physiologic effects of chemotherapeutic agents in psoriasis. J Invest Derm *33:* 357, 1959.
12. Woringer, Fr. & Wilhelm, E.: Action de la moutarde à l'azote dans le psoriasis. Bull Soc Franc Derm Syph *3:* 382, 1959.

*Received June 12, 1970*

Halvor Möller, M.D.
Department of Dermatology
Malmö General Hospital
S-214 01 Malmö
Sweden