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Variable responsiveness of generalized pustular psoriasis to treatment with dapsone and colchicine: report of 2 cases

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SUMMARY: **Variable responsiveness of generalized pustular psoriasis to treatment with dapsone and colchicine: report of 2 cases.**

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Introduction. *We attempt to critically review the relevant information on currently available unapproved indications of dapsone and colchicine in pustular psoriasis.*

Observations

Case 1: a 66-year-old woman had a 12 years history of pustular psoriasis. She had responded well to methotrexate treatment until we reach a cumulative dose of 1.48 g. A trial of dapsone was started for a new attack of her disease. The patient recovered after 2 weeks then she presented a relapse and a drop in hemoglobin level. Dapsone was stopped and we prescribed colchicine with good response. One month later, a new attack occurred.

Case 2: a 38-year-old man had severe generalized pustular psoriasis of 28 years' duration. Treatment modalities including acitretin methotrexate were applied, but induced short remissions. We try dapsone. At the third week, the patient did not show any significant clinical improvement. Afterwards, he was pyrexial, with red, painful, inflamed skin studded with monomorphic, sterile pustules. We stopped dapsone and prescribed acitretin at 25 mg/day and the lesions were cleared after 2 weeks.

Discussion. *Our present observations indicate that dapsone is not an effective and well-tolerated therapeutic option for patients with pustular psoriasis and that the effectiveness of colchicine is variable. A larger cohort with study design would be needed to draw further conclusions.*

RÉSUMÉ: **Reponse variable du psoriasis pustuleux generalisée au traitement par dapsone et colchicine: à propos de 2 cas.**

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Introduction. *Nous tentons de reconsidérer les indications de la dapsone et de la colchicine dans le psoriasis pustuleux étant donné que le niveau de preuve de leur efficacité dans cette dermatose est limité.*

Observations

Cas 1: une femme âgée de 66 ans présentait un psoriasis pustuleux depuis 12 ans. Elle répondait au traitement par méthotrexate jusqu'à ce qu'on ait atteint une dose cumulative de 1.48 g. Nous avons tenté la disulone pour une nouvelle poussée de maladie. Un blanchiment des lésions était obtenue après 2 semaines suivi d'une rechute avec anémie aigue. La dapsone a été arrêté. La patiente a été mise sous colchicine. Une rémission clinique était observé après 2 semaines. Elle développa une nouvelle poussée de psoriasis pustuleux généralisée après un mois de traitement.

Cas 2: un homme agé de 38 ans était suivi à notre consultation pour un psoriasis pustuleux évoluant depuis 28 ans. Différentes modalités thérapeutiques avaient été tentés tels que l'acitrétine et le méthotrexate et induisaient de courtes rémissions cliniques. Le patient était mis sous dapsone pour une poussée de psoriasis pustuleux généralisée. Aucune amélioration clinique ne fut obtenue après 3 semaines de traitement. Secondairement, le patient présentait un érythrodermie pustuleuse généralisée fébrile. La disulone a été arrêtée et nous avons prescrit l'acitrétine à la dose de 25 mg/j. Une rémission clinique était obtenue après 2 semaines de traitement.

Discussion. *Nous suggérons que la dapsone est inefficace dans le psoriasis pustuleux et expose à des incidents graves. L'efficacité de la colchicine est aléatoire. Une étude cohorte large est nécessaire pour tirer des conclusions.*

KEY WORDS: Postular psoriasis - Colchicine - Dapsone.
Psoriasis pustuleux - Colchicine - Dapsone.

Introduction

Pustular psoriasis is a rare form of psoriasis which is characterized by an eruption of sterile pustules. It can be divided into generalized and localized forms. Although not specifically licensed for this condition, dapsone and colchicine have been shown to be effec-

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tive in the treatment of some cases of extensive and recalcitrant generalized pustular psoriasis. We here report on the use of these drugs in two patients with pustular psoriasis.

This report attempts to critically review the relevant information on currently available unapproved indications of dapsone and colchicine in pustular psoriasis.

Case report

Patient 1: a 66-year-old woman had a 12 years history of pustular psoriasis but no other previous diseases worthy of note. Her dermatosis had been well controlled by acitretin until she was about 61 years-old. At this point, she developed a diffuse cutaneous desquamation associated with facial oedema, hepatic cytolysis, acute renal failure and hyperlipidaemia. The outcome was favourable after the discontinuation of acitretin. The pharmacologic study emphasized the imputability of this drug. Immediately afterwards, the patient had responded well to methotrexate treatment (10mg weekly) for 5 years. Subsequently, methotrexate therapy was stopped because we reach a cumulative dose of 1.48 g.

At this point, she presented a generalized pustular psoriasis. Given she cannot receive either acitretin or methotrexate; a trial of dapsone at 100 mg/day was started. Side effects were initially limited to nausea and vomiting. After 2 weeks of therapy, most of the patient's clinical signs had improved. Hemolytic anemia appeared during the first week (hemoglobin level was 12.3 g/dl before dapsone therapy; decrease to 9.5 g/dl after one week with reticulocytes count of 174080 cells/ml). So dapsone had had to be stopped for 2 days after which we tried again dapsone at 200 mg/daily. One week later, the patient presented a generalized pustular psoriasis and the hemoglobin level was 5.3 g/dl. This drop in hemoglobin was not tolerated by the patient. The symptoms included dizziness, dyspnea and headache. She needed urgently a transfusion to reduce blood loss. Haemoglobin level arises to 7.4 g/dl. The administration of dapsone was therefore stopped in the fourth week. One week after discontinuation, the haemoglobin level normalized.

A therapeutic trial with colchicine 1 mg/day was initiated. The skin lesions were almost cleared after two weeks. One month later, a new attack of generalized pustular psoriasis occurred.

Patient 2: the second patient was a 38-year-old man with severe, therapy-resistant generalized pustular psoriasis of 28 years' duration. Several conventional treatment modalities including acitretin and methotrexate were applied, but induced short remissions. Relapses became when the patient withdrawn his treatment, when the acitretin dose was reduced from 30 mg/day to 20 mg/day or were precipitated by infection. The multiple recurrent flares of pustular psoriasis and the large extension of the skin manifestations had required a number of hospital admissions and leading to a depression in our patient. We were prompted to try dapsone by earlier case reports who obtained dramatic improvement of pustular psoriasis in adults and children treated with this drug. We prescribed dapsone at 100 mg/day. At the third week, the patient did not show any significant improvement of the psoriatic lesions, the complete blood cell count was normal. Afterwards, the patient was pyrexial, dyspneic, and unwell. His exam showed a red, painful, inflamed skin studded with monomorphic, sterile pustule over the whole skin surface. White cell count was 23.5 10^9/L (78% neutrophils). Blood cultures were negative. The patient was admitted to intensive care. Central venous catheterization and parenteral nutrition was performed. He received amikacine/ciprofloxacine for 2 weeks. The pustular psoriasis settled over a period of 2 weeks with acitretin at 25 mg/day. He has subsequently been stabilized on a dose of 25 mg/day.

Discussion

Generalized pustular psoriasis (GPP) is a rare but notoriously recalcitrant cutaneous disease. Its etiology remains unknown. The severity of this disease and its response to each therapeutic modality vary among patients. Treatment options in GPP in adults include phototherapy, photochemotherapy and systemic agents (retinoids, methotrexate, ciclosporin).

Dapsone has been used successfully in the treatment of dermatoses with epidermal accumulation of neutrophils such as pustular psoriasis (8, 15). A considerable number of other inflammatory as well as bullous disease have been shown to respond in varying degrees to dapsone, although the drug is not licensed for them all (13).

In pustular psoriasis, the clinical data about the dapsone clinical results are based only on case reports. Mac Millan and Champion were the first to describe a clinical improvement of generalized pustular psoriasis in an adult treated with this drug (15).

Dapsone has been shown to inhibit chemotaxis (6), myeloperoxidase (7), as well as the production of toxic oxygen intermediates (3). Furthermore, it has been shown that dapsone suppresses neutrophil adherence to IgG- or IgA-coated epidermal basement membranes (12) and to albumin (2).

A recent article describes the inhibitory activity of dapsone and colchicine in a functional assay for neutrophil adhesion to epidermal cells. They suggest the possibility that the curative effects of dapsone in pa-

tients with neutrophilic dermatoses may be due to a general downregulation of the central functional integrin CD11b/CD18 on neutrophils (9).

Other investigators report a failure of pustular psoriasis to respond to sulfones as opposed to subcorneal pustular dermatosis and agree that this is a most reliable criterion to differentiate between these two diseases (14).

The cases presented here show differential responsiveness of pustular psoriasis to treatment with dapsone. One patient presented a clinical signs improvement during 2 weeks then she developed a new attack. In the other patient, a substantial therapeutic response was not observed. We decided to withdraw this drug because of a severe haemolytic anemia in one case and the outcome of a generalised pustular psoriasis (von Zumbusch) in the other case.

Colchicine has been also used successfully in the treatment of dermatoses with an involvement of neutrophils including pustular dermatoses (11). The drug affects hydroxyl radical and superoxide production (10), lysozyme release (5), chemotaxis (4), and may also have an effect on adhesion interactions (1). A recent simple assay evaluated that colchicine at concentrations of 10-200 ng/ml inhibited neutrophil binding with a clear correlation between inhibition and colchicine concentration (9).

Psoriasis was also one of the first cutaneous diseases treated with colchicine. Few earlier reports describe colchicine as an effective therapy for generalized pustular psoriasis. In one of the reports 3 of 4 patients experienced total remission after treatment for 2 weeks (11). Other studies have shown either minimal or no effect with the drug. These disparate results may be a reflection of the different doses employed and periods of administration. However, it is likely that colchicine has a limited therapeutic role in this pustular psoriasis (11). Patient 2 had shown a rapid initial improvement with colchicine, then he showed a relapse and pustular psoriasis was difficult to control with this drug.

Conclusion

Severe pustular psoriasis von Zumbusch type is a therapeutic challenge. If we take into consideration that the response to dapsone and colchicine therapy is unpredictable and that there is a significant toxicity profile associated with the use of dapsone, a complete understanding of the pharmacology of this drug and of which diseases are most likely to respond to treatment with dapsone and colchicine seems to be necessary. Our present observations indicate that dapsone is not an effective and well-tolerated therapeutic option for patients with pustular psoriasis and that the effectiveness of colchicine is variable.

References

1. KROLL*cine and methotrexate reduce leukocyte adherence and emigration in rat mesenteric venules*. Inflammation 1992;16:45-56.
2. BOOTH SA, MOODY CE, DAHL MV, et al. *Dapsone suppresses integrin mediated neutrophil adherence functions*. J Invest Dermatol 1992;98:135-140.
3. COLEMAN MD, SMITH JK, PERRIS AD, et al. *Studies on the inhibitory effects of analogues of dapsone on neutrophil function in-vitro*. J. Pharm Pharmacol 1997; 49:53-57.
4. CREASEY WA, BENSCH KG, MALAWISTA SE. *Colchicine, vinblastine and griseofulvin. Pharmacological studies with human leukocytes*. Biochem Pharmacol 1971;20:1579-1588.
5. HANEBERG B, GLETTE J, SORNES S, et al. *Influence of fever temperatures and of some cytoactive drugs on in vitro lysozyme release from monocytes and granulocytes*. Int J Immunopharmacol 1985;7:51-55.
6. HARVATH L, YANCEY KB, KATZ SI. *Selective inhibition of human neutrophil chemotaxis to N-formyl-methionyl-leucylphenylalanine by sulfones*. J Immunol 1986;137:1305-1311.
7. KAZMIEROWSKI JA, ROSS JE, PEIZNER DS, et al. *Dermatitis herpetiformis: effects of sulfones and sulfonamides on neutrophil myeloperoxidase-mediated iodination and cytotoxicity*. J Clin Immunol 1984;4:55-64.
8. MACMILLAN AL, CHAMPION RH. *Generalized pustular psoriasis treated with Dapsone.* Br J Dermatol 1973;88:183-185.
9. MODSCHIEDLER K, WELLER M, WÖRL P, et al. *Dapsone and colchicine inhibit adhesion of neutrophilic granulocytes to epidermal sections.* Arch Dermatol Res 2000;292:32-36.
10. SCHMIDT D, MORENZ E, MORENZ J. *Effect of drugs on superoxide formation by neutrophilic granulocytes*. Allerg Immunol 1987;33:95-100.
11. SULLIVAN TP, KING LE, BOYD AS. *Colchicine in dermatology*. J Am Acad Dermatol 1998;39:993-9.
12. THUONG NGUYEN V, KADUNCE DP, HENDRIX JD, et al. *Inhibition of neutrophil adherence to antibody by dapsone: a possible therapeutic mechanism of dapsone in the treatment of IgA dermatoses*. J Invest Dermatol 1993;100:349-355.
13. WOLF R, TUZUN B, TUZUN Y. *Dapsone: Unapproved uses or indications.* Clin Dermatol 2000;18:37-53.
14. WOLFF K. *Subcorneal pustular dermatosis is not pustular psoriasis*. Am J Dermatopathol 1981;3:381-2.
15. YU HJ, PARK JW, PARK JM, et al. *A case of childhood generalized pustular psoriasis treated with dapsone.* J Dermatol 2001;28:316-9.

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