SEQUENTIAL CLINICO-HISTOLOGICAL STUDIES IN PSORIASIS FOLLOWING METHOTREXATE THERAPY

S Talwar, VD Tiwari, R Lakhtakia, V Panvelkar

Ten cases of psoriasis were studied to see the pattern of histological resolution and to evaluate clinico-histological correlaion in psoriasis following weekly methotrexate therapy. Five sequential biopsies were taken in each patient. Scaling was first to regress followed by induration and erythema in 18, 26 and 35 days, respectively. Uniform granular layer appeared in 4 days, stratum corneum became orthokeratotic in 7 days, mitotic activity got restricted to basal layer in 7 days and rete ridges elongation was reduced to half in 11 days.Mild acanthosis, cellular infiltrate and vascular dilatation pesisted even after full clinical regression. Interestingly, 5 out of 10 biopsies revealed increase in cellular infiltrate and oedema after first methotrexate pulse.

Key Words: Psoriasis, Histopathology, Methotrexate

Introduction

Methotrexate is generally recognised as an effective drug in the treatment of psoriasis.[1,2] In this study, a sequential clinico-histopathological assessment was undertaken in an attempt to correlate the significant alterations during the period of treatment and the temporal framework in which they occurred.

Material and Methods

Ten new cases of extensive plaque psoriasis with average body area involvement of more than 40% were induced into the study. The cases selected were male with average age of 35 years having near similar constitution. All the cases were hospitalized during the period of study. Methotrexate was given orally in doses of 5 mg every 12 hours for three doses per week after proper evaluation of hepatic, renal and haematological function. Clinical examination was done daily for which erythema, induration and scaling were taken as assessment parameters. For histopathological examination well developed single large plaque on lower limb was selected and skin biopsies were taken from this lesion before starting methotrexate,4 and 6 days after first methotrexate pulse, 4 days after second methotrexate pulse and last biopay was performed from healed lesion with residual hyperpigmentation. In all, five biopsies were taken from the same lesion in each patient.

From the Departments of Dermatology and Pathology, Base Hospital, Lucknow, India.

Address correspondence to : Lt Col S Talwar C-219, Indira Nagar, Lucknow - 226016.

Results

1. All the cases responded to therapy requiring an average of 82.50 mg of methotrexate (4-12 methotrexate pulses). Scaling was first to regress followed by induration and erythema (Table I). The lesion healed with hyperpigmentation in about 35 days.

Table I. Clinical response following methotrexate therapy

Clinical parameters	Initial response (days)	Total clearance (days)
Scaling	7	18
Induration	10	26
Erythema	12	35

2. Some of the classical changes described in psoriasis[3,4] were missing in

some of the premethotrexate biopsies. Granular layer was present in patchy manner in 9 out of 10 pretreatment biopsies. This was evident in form of 1-2 cell layer thickness, specially in the interpapillary region. Patchy parakeratosis was evident in 3 out of 10 cases. Rete ridge enlargement was usually of 15-20 cell layer thickness while suprapapillary epidermis was of 3 cell layer thickness. Mitosis was seen in lower 3 epidermal cell layers. Dermal infiltrate was usually moderate and pradominantly lymphocytic. In one case good number of eosinophils were also seen. The detils of histologicl response following treatment (Table II) are:

Table II. Histopathological features before, during, and after methotrexate therapy.

Histopathological features	Pre treatment 1st pulse	4 days after pulse	Before 2nd 2nd pulse	4 days after	Clinical clearance
Parakeratosis	++	+	+	-	-
Granular Cell layer	+	Patchy	Uniform	Uniform	Uniform
Thining of supra-palillary epidermis	+	+	-	-	-
Rete ridge elongation	+++	+++	++	++	+
Mitosis (Cell layer)	3-4	2-3	1-2	1-2	1-2
Basal layer malanin	Melanin incontinence	Melanin incontinence	Melanin incontinence	Incre-assed melanin	Increased melanin
Dermal vessels dilatation	+++	+++	++	+	+
Dermal cellular infiltrate	+++	++++	+++	++	+

A. Changes in the epidermis

(a) Keratinisation and maturation: Parakeratosis, which was present in all the cases became patchy within 96 hours of the first dose and thereafter disappeared (Fig.1). The granular layer, which was either absent or patchy also recovered rapidly and in all the cases was continuous by third biopsy .

(b) Epidermal proliferation: In the suprapapillary regions the thinning returned to normal on the sixth day and clubbing and rete ridges elongation reduced by the 6th day. However, in most cases the elongation (acanthosis) persisted even after clinical recovery. Mitosis too were normal by 4-6 days.

(c) Basal layer: Breach of the basal layer in the form of melanin incontinence was present in the initial biopsy in three cases whereas the last biopsy invariably showed hyporpigmentation.

B. Changes in the dermis:

The dilated blood vessels and oedema reduced slowly but occasionaly persisted. The dermal infiltrate was seen in the mid dermis too by the 4th biopsy. Interestingly,in half the cases it had increased while on treatment and persisted, even if reduced, at the end of treatment. In all cases lymphocytes were present but in one case eosinophils were seen though there was no evidence of blood eosinophilia. Polymorphs were seen occssionally.

Discussion

The aetiopathogenesis of psoriatic

lesions remains unclear. Studies of relapsing lesions following stoppage of treatment reveal the earliest changes to be endothelial alteration, followed by appearance of degranulating mast cells and then marked macrophage infiltration in the basal keratinocytes.[5] These changes procede the charactersitic opidermal changes.[4]

Methotrexate acts in psoriasis competitive inhibition of dihydrofolate reductase, inhibition of (5a-induced polymorphonuclear chemotaxis,[6] leucotrine-84) induced infiltration of granulocyte into psoriatic epidermis,[7] and immunosuppressive effect.[8]

In the present study, the initial change noted uniformaly was the disappearance of parakeratosis and the reappearance of the granular layer, implying that it is the correction of the steps of abnormal maturation that seem to occur first. Whereas, the slower rate of recovery of the normal thickness of epidermis signifies that the actual rate of proliferation is controlled at a much slower rate. Thus, methotrexate probably acts on differentiation as well as by reducing proliferation rate.

Though melanin incontinence was present only in few cases, the process of recovery by hyperpigmentation appears to be a part of the normal healing process with incressed activity of the melanocytes.

Recovery of the vascular changes is slow and may account for the relapses where such lesions are not treated long enough, as according to some studies,[5] they appear to be the starting point for the entire lesion to develop.

Though methotrexate is known to suppress polymorphonuclear chemotaxis intraepidermally,[6] these cells have been found to appear while on treatment by some authors.[9] But, in this study, though these cells were seen only occasionally, the increase in density of the chronic inflammatory response appears to be favourable as it begins after the first pulse of therapy and though dininished, persists even later. The presence of eosinophils is an unusual feature which is difficult to explain.

This pilot study indicates that some features like reversion to orthokeratosis and appearance of granular layer may be the earliest and consistent signs of improvement. Likewise the persistance of vascular changes, acanthosis and dermal inflammation as noticed by other workers[10] may be taken to indicate that a histological assessment be made prior to labelling a case as clinically cured and switching over to maintainence therapy.

References

1. Roenigk R, Auerbach R, Maiback H et al. Methotrexate in psoriasis: revised guidelines. J Am Acad Dermatol 1988; 19: 145-56.
2. Talwar S. Methotraxate-PUVASOL combination in treatment of psoriasis/ Ind J Dermatol Venereol Leprol 1992; 58:25-9.
3. Lever WF, Lever GS. In: Histopathology of the Skin, 7th edn. USA: JB Lipincott Company 1989, 156-64.
4. Ragaz A, Ackerman AB. Evolution, maturation and regression of lesions of psoriasis. Am J Dermatopathol 1979; 1: 199-214.
5. Schubert C, Christophers E. Mast cells and macrophages in early relapsing psoriasis. Arch Dermatol Res 1985; 277: 352-8.
6. Ternewitz T, Bjerring P, Anderson P, et al. Methotrexate inhibitis the human C5a-induced skin response in psoriasis patients. J Invest Dermatol 1987; 89: 192-6.
7. Van de Kerkhof P, Bauef F, Grooth RM. Methotrexate inhibits leukotrione B4-induced intraepidermal accumulation of polymorphonuclear leukocytes. Br J Dermatol 1985; 113: 215a-255a.

8. Epstein W, Mailback H. Immunologic competence of patients with psoriasis receiving cytotoxic drug therapy. Arch Dermatol 1965; 91: 599-606.

9. Moller H. Reactivation of acute inflammation by methotrexate, J Invest Dermatol 1969; 52: 437-41.

10. Lal S, Sadana SR, Chitkara NL. Histopathology of psoriasis at various stages. Ind J Dermatol Venereol Leprol 1965; 31: 216-22.