

# An Open-Label, Single-Arm Pilot Study in Patients with Moderate to Severe Plaque-Type Psoriasis treated with Mesalazine

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## ABSTRACT

Lipoxygenase inhibitors have been reported to have a therapeutic effect in psoriasis. Mesalazine, a lipoxygenase inhibitor, similar to sulfasalazine was tried in psoriasis. Patients with moderate to severe psoriasis were treated with mesalazine in a dose of 400 mg thrice a day for 8 weeks. Patients were assessed for disease activity at the start of therapy, at 4 weeks and at 8 weeks using the psoriasis area severity index (PASI). Twenty-one patients (18 males and 3 females) of stable plaque psoriasis with a mean age of 42.3 years were included in the study. Duration of disease ranged from 3 months to 30 years. Mean body surface area involved was 36.3%. Of 19 patients who completed the study, 7 (36.8%) had >40% decline in PASI. Two patients did not respond to therapy. Mean baseline PASI decreased from 16.2 to 13.2 at 4 weeks and 10.1 at 8 weeks ( $p < 0.01$ ). Both the values were statistically significant. Mesalazine can prove to be a significant addition or adjunct to the systemic therapies available for the treatment of psoriasis.

**Keywords:** Psoriasis, Lipoxygenase inhibitor, Mesalazine.

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## INTRODUCTION

Psoriasis is a genetically determined, chronic inflammatory skin disorder that still eludes cure. Both conventional and systemic modalities used in the treatment of psoriasis have their limitations like hepatotoxicity associated with methotrexate, mutagenic potential of PUVA and skeletal and teratogenic effects of retinoids. The scope for newer safe and effective systemic therapies in psoriasis is hence immense. Elevated levels of arachidonic acid<sup>1</sup> along with increased 5 and 12-lipoxygenase activity resulting

in increased production of eicosanoid mediators of inflammation (LTB<sub>4</sub>) have been found in psoriatic skin.<sup>2</sup> Sulfasalazine-a potent 5-lipoxygenase inhibitor has been found to be therapeutically effective in both psoriasis and psoriatic arthritis.<sup>3-7</sup> A topical 5-lipoxygenase inhibitor (Lonapalene) has also been reported to have therapeutic effect in psoriasis.<sup>8</sup> Mesalazine or 5-aminosalicylic acid (5-ASA), is the effective split product of sulfasalazine. It has improved tolerability and a reduced incidence of side effects like bone marrow suppression and decreased sperm counts. This prompted us to study if mesalazine could be used with benefit in cutaneous psoriasis.

## MATERIALS AND METHODS

Adult patients with moderate to severe plaque-type psoriasis for at least 6 months which involved at least 10% of the body's surface area were enrolled in the study. The patients were candidates for systemic therapy or phototherapy and could not be managed by topical therapy. Patients with clinically relevant gastrointestinal, hepatic or renal disorders, and those with unstable metabolic or endocrine disorders, were excluded, as were those with systemic or generalized infections, or a history of malignancy. The patients had not received other systemic disease modifying drugs or phototherapy within 28 days, or topical therapy within 14 days of starting mesalazine. Women of childbearing potential had to have a negative urine pregnancy test at screening, and agree to use two forms of contraception throughout the study. Men agreed to use barrier contraception while on study medication. All patients provided written informed consent before entering the study, and the protocol was approved by the department review board.

*The study consisted of three phases:* A 28-day screening phase, 8 weeks treatment period where patients received mesalazine 400 mg tid and a 4 weeks observational follow-up phase to assess for psoriasis relapse and flare. The patients were instructed not to use any additional medications for psoriasis during the treatment phase except antihistamines, nonmedicated emollients and shampoos.

The patients were recruited over a period of 2 years and all of them underwent a pretreatment evaluation

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consisting of a detailed clinical assessment, determination of psoriasis area and severity index (PASI) and routine laboratory evaluation including complete blood counts, renal function tests, fasting blood sugar, liver function tests, serum amylase, X-ray chest and urine examination. The PASI was determined at baseline (week 0) and repeated after 4 and then at 8 weeks of treatment. At each scoring visit, patients were examined clinically, PASI scoring was done and they were questioned regarding any adverse effects of therapy.

The primary efficacy endpoint, prospectively defined in the protocol, was the change from baseline to PASI at 8 weeks of treatment. Secondary variables were the change in individual parameters like mean scores of erythema, induration and scaling area during the study period.

Paired T-test was used to analyze the data.

## RESULTS

Twenty one patients (18 males and 3 females) aged 19 to 62 years (mean—42.3 years) were enrolled in the study. Two patients did not report for follow-up and hence were excluded from the study. Nineteen patients completed the study. All the patients had moderate to severe stable plaque psoriasis. Duration of disease ranged from 3 months to 30 years. Mean body surface area involved was 36.3%. None of the patients had psoriatic arthritis. Baseline PASI score of the patients ranged from 3.3 to 29.8 (mean 16.2, SD 6.8). At the end of 8 weeks of mesalazine therapy a fall in PASI was seen in 17 patients. Two patients did not show any decline in PASI. The percentage fall in PASI was as follows—PASI at 8th week decreased by 40 to 75% (good improvement) in 7 patients, by 25-39% (moderate improvement) in 6 patients and by less than 25% (minimal improvement) in 4 patients. The mean baseline PASI decreased from 16.2 to 13.2 at 4 weeks (SD 6.9) ( $p < 0.01$ ) and to 10.1 at 8 weeks (SD 6.2) ( $p < 0.01$ ) while the median baseline PASI decreased from 16.6 to 12.9 at 4 weeks and 8.4 at 8 weeks (Fig. 1). The fall in median value of PASI at 4 and 8 weeks was also statistically significant. In order to study the effect of mesalazine in more detail, individual parameters like mean scores of erythema, induration, and scaling area were also observed. The time dependent analysis of these parameters indicated that erythema, induration and scaling were all affected and decreased at the end of 8 weeks (Fig. 2). This corresponded to the reduction in mean and median PASI scores. None of the patients reported any major side effects except for nausea in 3 (15.8%), at the initiation of therapy, which subsided, with the continuation

of the drug. The drug was well tolerated and no alteration in CBC, blood urea and creatinine and serum amylase was seen in any of the patients.

## DISCUSSION

Mesalazine (5-Aminosalicylate) is one of the mainstays in the treatment of inflammatory bowel disease (IBD). It has also been found effective in the management of urticaria, pyoderma gangrenosum and psoriasis.<sup>9,10</sup> The proposed mechanisms for its anti-inflammatory properties are inhibition of 5-lipoxygenase, cyclooxygenases, nuclear factor-kappa B activation, T lymphocyte proliferation and antigen stimulated histamine release. Studies on sulfasalazine<sup>3-7</sup> have confirmed the efficacy of lipoxygenase inhibitors in the treatment of psoriasis. Eight weeks of sulfasalazine therapy led to a significant reduction in keratinocyte intercellular adhesion molecule-1 expression; reduction in both intraepidermal and dermal T lymphocytes; along with LTB4 in urticaria.<sup>9</sup>

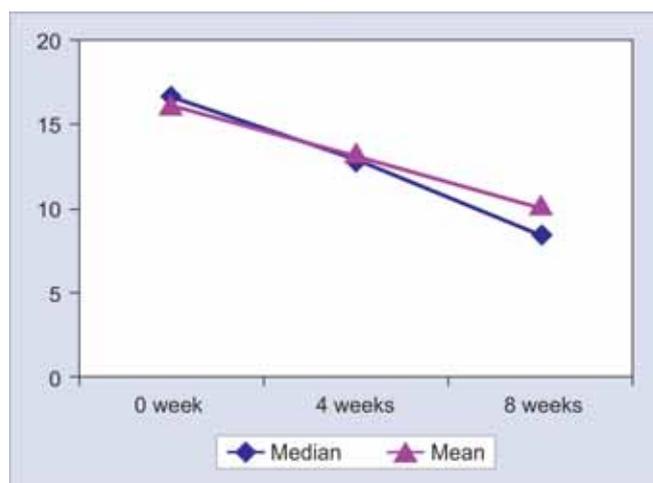


Fig. 1: Reduction in mean and median PASI scores observed during the study

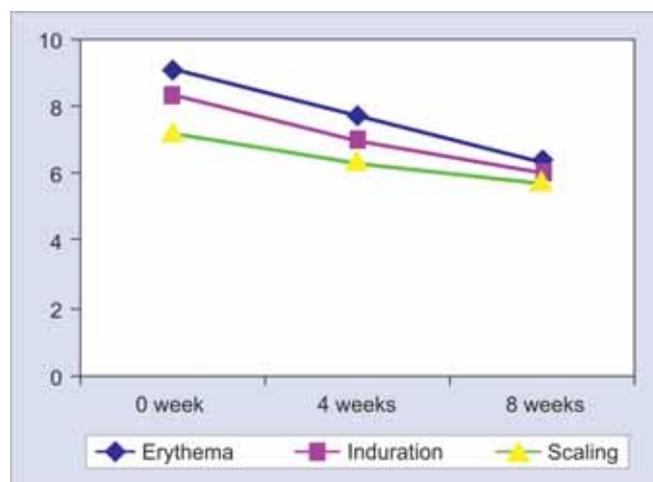


Fig. 2: Changes in parameters like erythema, induration and scaling during the study

Hypersensitivity reactions, bone marrow suppression and decreased sperm count that may be associated with the use of sulfasalazine due to its sulphapyridine moiety are not seen with mesalazine. The clinical efficacy of mesalazine in our trial was almost similar to that of sulfasalazine observed in other studies. Although increased risk of interstitial nephritis and pancreatitis has been reported with the use of mesalazine; none of our patients had any adverse reaction to mesalazine.

All those patients who demonstrated a positive response started exhibiting clearance of lesions by 4th week and significant therapeutic response was visible at the completion of 8 weeks. More than 50% decrease in PASI (PASI 50) was seen in 33.3% patients and additional clearance was noted at 12th week even after the drug had been stopped in these patients.

The therapeutic result seen with mesalazine in our study is undeniably modest, but it is comparable to that seen with newer expensive drugs like mycophenolate, tacrolimus and pimecrolimus which are also not free from side effects.<sup>10,11</sup> Since the patient number was less it is not possible for us to comment about any definite predictors of outcome. Mesalazine is an immunomodulatory and an anti-inflammatory drug, inhibiting interleukin 2 release and inflammatory cell chemotaxis, with comparatively few serious side effects. We observed that mesalazine produced a significant reduction in psoriasis severity, at doses of 400 mg tid and it was well tolerated. However, studies of longer duration in larger number of patients are needed to fully assess the efficacy and safety of mesalazine in psoriasis.

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