The evaluation of efficacy and safety of methotrexate and pioglitazone in psoriasis patients: A randomized, open-labeled, active-controlled clinical trial

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Abstract:

OBJECTIVES: Psoriasis is a chronic inflammatory disease showing co-existence with metabolic syndrome (MS), as has been confirmed by numerous epidemiologic studies in recent times. In this study, the aim was to ascertain the beneficial effects of pioglitazone in psoriasis, simultaneously targeting the improvement of MS parameters.

MATERIALS AND METHODS: We conducted a prospective randomized open-labeled parallel-group interventional study in patients of moderate-to-severe chronic plaque psoriasis. A total of 90 patients were inducted in study and divided into three groups of standard treatment (methotrexate 7.5 mg/week for 12 weeks), active treatment (pioglitazone 15 mg tablets once daily for 12 weeks), and their combination. Primary outcome was taken as percentage Psoriasis Area and Severity Index (PASI) improvement from baseline; secondary outcomes were PASI-75, safety profile, and MS parameters.

RESULTS: Intergroup evaluation of PASI score showed that standard treatment methotrexate and active treatment pioglitazone were comparable. Combination of methotrexate and pioglitazone proved superior in efficacy from both standard and active treatment in 8 and 12 weeks. Adverse drug reactions were mild and treated symptomatically. Pioglitazone and combination group also demonstrated beneficial efficacy in parameter of MS hence establishing it as a potential therapy in psoriasis with MS.

CONCLUSIONS: Pioglitazone alone or in combination with standard treatment may be a safe alternative drug for psoriasis coexisting with MS proving beneficial for both.

Keywords: Chronic plaque psoriasis, metabolic syndrome, methotrexate, pioglitazone

Introduction

Psoriasis is a chronic inflammatory, multifactorial condition found in 2%-3% of global population. It is an immune-mediated ailment commonly seen in genetically predisposed individuals triggered by environmental factors affecting mainly the skin, nails, and joints. Apart from the cutaneous manifestations, the substantial cost of treatment adds to the psychosocial burden and has a negative effect on the quality of life.

In psoriasis, the main pathophysiology is excessive epidermal cell multiplication and keratinization due to disturbed T-cell function which manifests as erythema, indurations, and scaling. There are many assessment tools for psoriasis, the gold standard being...
the Psoriasis Area and Severity Index (PASI). It measures the extent of erythema, indurations and scaling on a grading scale from 0 to 4 along with the involvement of four anatomical regions.\[2\]

Based on the etiopathogenesis, various treatment options comprise of topical or systemic medications, phototherapy, and biologic agents. Topical treatment includes emollients, topical steroids, tar preparations, and Vitamin D and A analogs. Conventional systemic therapies include acitretin, cyclosporine, and methotrexate. Newer biologic agents approved for use in psoriasis are infliximab, adalimumab, etanercept, ustekinumab, secukinumab, and ixekizumab. These newer drugs have severe side effects, high cost factor, and lack of long-term safety data which limits their usage in general population.\[3\]

Psoriasis being a chronic inflammatory disease, involves many cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-a) which predisposes toward the development of metabolic syndrome (MS). There are several studies confirming the association of psoriasis and MS as both shows a common inflammatory pathway. This association was first demonstrated by Henseler and Christophers in 1995.\[4\] Subsequently, many researchers demonstrated this association. Gisondi et al. in 2007, demonstrated a higher prevalence of MS in psoriasis patients using the National Cholesterol Education Program Adult Treatment Panel (ATP) III criteria.\[5\] Nisa and Qazi also showed the frequency of MS as 28% in psoriasis patients as compared to 6% in control group.\[6\] In concordance to the above studies, Zindancı et al. also demonstrated the prevalence of MS in psoriasis patients using the International Diabetes Federation criteria.\[7\]

The core pathophysiology involved is the common inflammatory pathways and genetic predilection. The T-cell-mediated inflammation leads to overexpression of TNF-a, IL-6, adiponectins, etc., which leads to epidermal hyperplasia in psoriasis, modifies adipokine expression, alters insulin signaling thus promoting insulin resistance, obesity, and dyslipidemia. All these factors further predispose the patient to diabetes, hypertension, angiogenesis, and cardiovascular disorders.

The diagnostic criteria of MS as issued by ATP III which includes the presence of any 3 of the ensuing factors abdominal obesity (waist circumference >102 cm in men; >88 cm in women), elevated serum triglyceride (TG) (>150 mg/dl or under treatment), low high-density lipoprotein (HDL) cholesterol (<40 mg/dl in men; <50 mg/dl in women or under treatment), elevated blood pressure (BP) (>130/85 mmHg or under treatment), and elevated fasting plasma glucose (>100 mg/dl or under treatment).\[8\] Both the diseases are reciprocally related as the presence of psoriasis may induce MS or MS may aggravate psoriatic inflammation.

Thus, the treatment of psoriasis should not only focus on reducing psoriatic inflammation but should also control the risk factors of MS. Although the newer biologic agents currently being used in psoriasis have good efficacy only in psoriasis the restrictive aspects are safety issues and cost factor which limits their usage. Moreover, these drugs do not have any conclusive evidence of controlling MS. Hence, we tried to explore a therapy which could be beneficial both in managing psoriasis as well as reducing predisposition to MS. Thiazolidinediones is one such group of drugs which is being explored in psoriasis. The foremost report of thiazolidinedione curing psoriasis was in a three patient open-label study where troglitazone was being used for the treatment of uncontrolled diabetes mellitus but concurrently showed significant improvement in psoriatic lesions as well.\[9\] Subsequently, many case reports/case series and short-term trials demonstrating therapeutic efficacy of glitazones on psoriasis have been published.\[10-12\]

Thiazolidinediones are peroxisome proliferator-activated receptors agonists which have a wide array of functions such as improving glycemic control by enhancing insulin sensitivity in liver, fat and muscle. They also regulate hemoglobin A1c levels and cause β-cell protection. Apart from improving insulin sensitivity, it also has an anti-inflammatory effect in cardiovascular diseases.\[13\] It suppresses cardiac inflammation and fibrosis and decreases vascular endothelial dysfunction by reducing reactive oxygen species.\[14\] Pioglitazone also shows antiatherogenic and vasculoprotective effect\[15\] and significantly improved the endothelial functions in diabetic patients.\[16\]

Although many older and newer efficacious drugs were being used in psoriasis none was effective in controlling MS concurrently occurring with psoriasis. Hence, we planned this study to determine the efficacy of pioglitazone in psoriasis as it showed some beneficial effect in MS as well.

Materials and Methods

We conducted this study at our teaching institute after taking permission from institutional ethics committee. This study was a prospective randomized, open-labeled, parallel-group active treatment controlled interventional study of 12 weeks’ duration. Clinical trial registration was obtained as per regulatory requirements. Patients of both sexes in the age group of 18–65 years with moderate-to-severe chronic plaque psoriasis (body surface area involvement ≥10%).\[17\]
attending the dermatology outpatient department (OPD) in our college were screened according to their eligibility criteria in the study.

**Inclusion criteria**
- Patients of either sex aged 18–65 years
- New cases of moderate-to-severe plaque psoriasis vulgaris ≥10% (apart from palmoplantar psoriasis which will be included)
- Older cases of plaque psoriasis vulgaris showing relapse after 4 weeks of stopping the systemic treatment or patients who have left the treatment for 4 weeks or more due to compliance or monetary issues (all patients were responders to previous therapy-methotrexate + topical steroid).

**Exclusion criteria**
- Erythrodermic, pustular, or guttate psoriasis
- Liver disease, cardiac disease (history of congestive heart failure), renal failure, or any other major medical disorders detected by history
- Pregnancy and lactation
- Known contraindication to pioglitazone or methotrexate
- Patient with active bladder cancer or with a prior history of bladder cancer and having uninvestigated hematuria
- Patient with previous exposure to chemotherapeutic agents, such as cyclophosphamide or previous irradiation of pelvic region.

Patients were randomized into three groups after taking written informed consent.
- Group A: Standard treatment group – methotrexate 7.5 mg/week for 12 weeks
- Group B: Active treatment group – pioglitazone 15 mg tablets once daily for 12 weeks
- Group C: Combination therapy – methotrexate 7.5 mg/week for 12 weeks + pioglitazone 15 mg tablets once daily for 12 weeks.

Folic acid supplementation was given in Groups A and C to counter or minimize the adverse effects of methotrexate. In addition to these treatments, topical therapy in all the groups was the same. Clobetasol + salicylic acid tube was given to the patient and asked to apply in the morning and evening on affected lesions. The patients were educated on how to apply the ointment as Finger Tip Unit (FTU) as 1 FTU covers two adult hands. Antihistaminics were given as per need. Follow-ups are done on 4th, 8th, and 12th weeks.

The primary outcome measure was efficacy in terms of treatment success, detected as clinical improvement of skin condition and percentage PASI improvement from baseline. PASI is the most extensively used tool for the measurement of the severity of psoriasis. PASI includes the assessment of the severity of lesions and the area involved in a single score in the range 0 (no disease) to 72 (maximal disease).[18] The secondary outcome measures were PASI improvement by at least 75% from baseline (PASI-75), safety of the combination therapy as measured by any unexpected adverse effects and MS parameters.

The investigations done were complete blood counts, platelet count, blood sugar, liver function tests, and renal function test. All these investigations were done at baseline (0 weeks) and repeated every 4 weeks. Clinical examination was also done every 4 weeks. However, additional test for MS, i.e., waist circumference, serum TG, HDL cholesterol, and BP were measured at baseline, i.e., 0 week and at the completion of study at 12 weeks.

The statistical analysis was done among three groups by one-way ANOVA-F-test followed by Tukey’s multiple comparison test at 5% significance level. Paired t-test was applied in diagnostic criteria for MS, and P < 0.05 was considered statistically significant.

**Results**

This study was done prospectively in dermatology OPD. Ninety-eight patients of moderate-to-severe chronic plaque psoriasis were screened, out of which eight patients did not meet the inclusion criteria, hence 90 patients qualified for the study. These patients were randomly allocated in each of the three groups as mentioned above. Twenty-nine patients completed follow-up in Group A, as one patient discontinued intervention due to compliance issues. All 30 patients recruited in Groups B and C completed follow-up [Figure 1]. Baseline characteristics evaluated at 0 week such as gender distribution, age, body surface area involved and baseline PASI score were all comparable.

Mean PASI score in all three groups was evaluated by ANOVA showing that there was no significant difference in treatment Groups at 0 and 4 weeks but was statistically significant at 8 and 12 weeks demonstrating the efficacy of treatment at 8 and 12 weeks [Table 1 and Figure 2]. Clinical improvement of skin condition by PASI reduction range <50, 50–75, and >75 were calculated after 12 weeks showing maximum number of patients in PASI >75 range in all three treatment groups, but there was 100% improvement in Group C, i.e., combination treatment group after 12 weeks [Table 2].

Further evaluation of PASI Score to see intergroup difference was done by Tukey’s multiple comparison test. When standard Group A (methotrexate) was compared with Group B (pioglitazone) at 0, 4, 8, and
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Table 1: Mean Psoriasis Area and Severity Index scores in three groups at 0, 4, 8, and 12 weeks

| Weeks | Group A (score±SD) | Group B (score±SD) | Group C (score±SD) | Intergroup comparison by ANOVA: F (P) |
|-------|-------------------|-------------------|-------------------|---------------------------------------|
| 0     | 17.68±1.103       | 17.73±1.203       | 18.12±1.419       | 1.310 (0.275)                         |
| 4     | 11.86±1.062       | 11.75±1.486       | 11.87±1.317       | 0.0728 (0.929)                        |
| 8     | 6.717±1.026       | 6.723±1.428       | 5.807±1.069       | 5.865 (0.004)*                        |
| 12    | 3.797±0.6185      | 4.540±1.467       | 3.063±0.6178      | 13.91 (<0.0001)*                      |

Data presented as mean±SD. *Statistically significant difference using ANOVA. SD=Standard deviation

12 weeks, there was no statistically significant difference in treatment outcomes showing that the active treatment pioglitazone was comparable to standard treatment methotrexate. When standard Group A (methotrexate) and Group B (pioglitazone) were contrasted with Group C (combination of methotrexate + pioglitazone), there was no significant difference in treatment efficacy at 0 and 4 weeks, but treatment efficacy was statistically...
significant at 8 and 12 weeks demonstrating the higher efficacy of combined usage of methotrexate and pioglitazone at 8 and 12 weeks [Table 3].

The assessment of MS criteria by paired *t*-test at baseline and 12 weeks showed that in Group A there was a nonsignificant reduction in waist circumference whereas in Group B and C, there was a significant reduction in waist circumference. On measuring TG levels, there was nonsignificant increase in TG levels in Group A, but in Groups B and C, there was a nonsignificant decrease in TG levels. HDL levels show nonsignificant increase in Group A but a significant decrease in Group B and C. BP measurement demonstrated that Group A had nonsignificant decrease whereas Group B and C had a significant decrease. Fasting plasma glucose levels revealed a nonsignificant increase in Group A but a significant decrease in Group B and C [Table 4].

The adverse drug profile was mild and self-limiting in all the three groups. On assessing the adverse drug reactions (ADRs), Groups A and B had five patients each, and in Group C only eight patients experienced mild ADR [Table 5]. The causality assessment was done by Naranjo Probability Scale and all reactions were probable or likely. All these patients were treated symptomatically and their symptoms subsided.

**Discussion**

Psoriasis is an immunological disease-causing release of cytokines, promoting immune-mediated response in skin leading to excessive epidermal proliferation and chronic inflammation of the skin. Systemic treatment options of psoriasis have advanced due to a better understanding of underlying pathophysiology. There is a strong correlation between psoriasis and MS as many inflammatory pathways and genetic predispositions are common in both the disease. This has been proved by numerous studies.[5,19]

Systemic therapies especially biologics may reduce the inflammatory and immune component of the disease but they do not target other components of MS. Moreover, their cost factor, safety and tolerability profile may also limit their future use. Hence, in this study, we have tried to assess the role of pioglitazone, a peroxisome

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**Table 2: Efficacy of treatment as assessed by Psoriasis Area and Severity Index score after 12 weeks**

| PASI score reduction range | PASI <50 | PASI 50-75 | PASI >75 | Percentage PASI improvement from baseline |
|----------------------------|---------|-----------|---------|------------------------------------------|
| Group A (n=29)            | 0       | 5         | 24      | 78.54±3.130                              |
| Group B (n=30)            | 1 (3.33)| 9 (30)    | 20 (66.66)| 74.20±9.346                              |
| Group C (n=30)            | 0       | 0         | 30 (100)| 83.16±2.649                              |

*PASI=Psoriasis Area and Severity Index

**Table 3: Intergroup comparison of Psoriasis Area and Severity Index scores**

| Criteria for metabolic syndrome | Group A versus Group B | Group A versus Group C | Group B versus Group C |
|--------------------------------|------------------------|------------------------|------------------------|
| Waist circumference | 1.977 (>0.05) | 1.977 (>0.05) | 1.977 (>0.05) |
| TG (mg/dl) | 0.047 (>0.05) | 0.4907 (>0.05) | 0.4390 (>0.05) |
| HDL cholesterol (mg/dl) | 4.156 (<0.05*) | 4.220 (<0.05*) | 0.0278 (<0.05*) |
| BP | 6.441 (<0.05*) | 6.441 (<0.05*) | 0.0 (>0.05) |

*Statistically significant difference using Tukey’s multiple comparison test

**Table 4: Metabolic syndrome parameters**

| Criteria for metabolic syndrome | Group A (n=29) | Group B (n=30) | Group C (n=30) |
|--------------------------------|----------------|----------------|----------------|
| Waist circumference | 8.562 (<0.0001)* | 9.928 (<0.0001)* | 9.898 (<0.0001)* |
| TG (mg/dl) | 7.999 (<0.0001)* | 6.810 (<0.001)* | 12.65 (<0.0001)* |
| HDL cholesterol (mg/dl) | 6.857 (<0.001)* | 7.279 (<0.001)* | 6.148 (>0.05) |
| BP | 8.610 (<0.001)* | 7.279 (<0.001)* | 6.148 (>0.05) |
| Fasting plasma glucose (mg/dl) | 9.282 (<0.0001)* | 9.143 (<0.0001)* | 10.143 (<0.0001)* |

*Statistically significant difference using paired *t*-test. BP=Blood pressure, HDL=High-density lipoprotein, TG=Triglyceride
proliferator-activated receptor-gamma (PPAR-γ) agonist used alone as well as in combination with the standard treatment methotrexate in psoriasis patients.

In our study, standard treatment methotrexate and active treatment pioglitazone were comparable in efficacy demonstrating pleiotropic effects of pioglitazone. By acting as an agonist on PPAR-γ receptors, it has an anti-inflammatory response and decreases the formation of inflammatory mediators especially cytokines and infiltration of inflammatory cells. PPAR-γ receptors belong to superfamily of steroid nuclear receptors and reportedly improve insulin sensitivity, lower BP, improve lipid profile, and endothelial functions indicating a favorable improvement in cardiovascular status. These receptors are also expressed on human keratinocytes, and its agonist inhibits the growth and proliferation of normal and psoriatic keratinocytes in culture, thereby demonstrating antiproliferative properties. Another study in murine model showed decreased epidermal keratinocyte proliferation using thiazolidinediones topically. From these studies, we can derive that thiazolidinediones may serve as promising therapy in psoriasis patients.

Moreover, pioglitazone also improved the parameters of MS, hence may provide a dual purpose therapy in psoriasis as most cases may have an associated MS. Some initial studies also demonstrated the clinical efficacy of pioglitazone in psoriasis though it was on a small number of patients.

Our study corroborated the findings of a pilot study done in 2005 with pioglitazone 15 mg and 30 mg versus placebo in patients with plaque psoriasis which demonstrated the efficacy of pioglitazone in a 10-week trial as compared to placebo.

Later, a meta-analysis showed that rosiglitazone had a nonsignificant improvement of PASI 50/70 in pooled analysis, but pioglitazone showed significant efficacy. Our study was in confirmatory to this study. A study by Singh and Bhansali also confirmed the efficacy of pioglitazone in psoriasis patients with MS.

Our study also highlighted that a combination of methotrexate + pioglitazone showed a statistically significant difference in treatment efficacy at 8 and 12 weeks but not at 0 and 4 weeks as compared to both methotrexate and pioglitazone individually, illustrating that combination was more effective than standard methotrexate and active drug pioglitazone. This result was in conformity to the study conducted in 2015 by Lajevardi et al. which also confirmed the better reduction in mean PASI score using a combination of pioglitazone and methotrexate in plaque-type psoriasis. They took lesser number of patients as compared to our study and there was no separate active treatment group of pioglitazone as in our study thus increasing the validity of our study.

Studies have also proven that the PPAR-γ agonists including thiazolidinediones also hindered the production of a number of inflammatory cytokines from macrophages and T lymphocytes, especially TNF-α, which has been proposed to be a major pathogenic mediator of psoriatic lesions. Pioglitazone may enhance the efficacy of methotrexate as both the drugs have anti-inflammatory, antiproliferative, and immunomodulatory effects specifically suppressing keratinocyte proliferation and thus having enhanced antipsoriatic effect. Pioglitazone being a safe drug and having a wide array of pleiotropic effect such as in diabetes, hypertension, and MS, thus may also be used in psoriasis as it usually co-exists in such patients. Moreover, if used in combination with methotrexate, we can use low doses of the standard drug preventing its harmful side effects. Both the standard drug and test drug were found to be safe in our study. Only few patients had side effects that too were mild and treatable not posing any risk to the patient.

Our study has certain advantages. The duration is taken as 12 weeks which is sufficient to see the response of treatment in psoriasis. Furthermore, standard therapy, active treatment group, and combination group are kept separate and each is compared with each other. The study also has some limitations. Our study was not associated with any mechanistic exploration for combined higher effects. We used only the lowest and safest dose of pioglitazone 15 mg. Further evaluation by higher doses could elucidate the dose-response relationship. Furthermore, we used low doses of methotrexate which is safe enough.

**Conclusions**

The present study elaborates on the beneficial effect of pioglitazone in plaque psoriasis and is comparable to the present standard treatment methotrexate. Moreover, pioglitazone is much safer and more beneficial in patients...
of MS which is now showing a high prevalence coexisting with psoriasis. Furthermore, pioglitazone enhances the efficacy when combined with methotrexate and can be an effective and safe alternative to combine with methotrexate than other immunosuppressive agents. Thus, we advocate the use of pioglitazone in psoriasis patients who are not tolerating other drugs as a safe alternative either alone or in combination. Although higher doses and long-term safety still needs to be ascertained.

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**Conflicts of interest**
There are no conflicts of interest.

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