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Research Article

EVALUATION OF EFFICACY AND SAFETY OF ORAL VITAMIN D_3 AND VITAMIN E AS AN ADD-ON-THERAPY TO METHOTREXATE IN PATIENTS OF MODERATE CHRONIC PLAQUE PSORIASIS

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ABSTRACT

Objective: This study was conducted with the aim to evaluate the efficacy and safety of oral Vitamin D_3 and Vitamin E as an add-on-therapy to methotrexate (MTX) in patients of moderate chronic plaque psoriasis.

Methods: In this prospective, open-labeled, randomized and comparative clinical study, a total of 120 patients aged 20–60 years with moderate chronic plaque psoriasis, attending the dermatology outpatient department, were randomly allocated into three groups, i.e., Group M, Group D, and Group E, each consisting of 40 patients. Group M received MTX (7.5 mg) tablet orally weekly, Group D received MTX (7.5 mg) and Vitamin D_3 (60,000 IU) sachet orally weekly, and Group E received MTX (7.5 mg) weekly and Vitamin E (400 mg) daily. Efficacy assessment was done through the following primary parameters-psoriasis area and severity index (PASI) score, dermatology life quality index (DLQI), and psoriasis disability index (PDI), and secondary parameters such as vitamin D deficiency and insufficiency among the study participants and improvement of serum 25(OH)D concentration. Adverse events were monitored.

Results: PASI and DLQI were calculated at the time of recruitment (baseline), 1 month, 2 months, 3 months, and 4 months, and PDI and serum Vitamin D were calculated at baseline and 4 months. On intergroup comparison of PASI score and PDI, statistically significant results were seen at 4 months. DLQI showed significant results at 2, 3, and 4 months. Significant results were observed in Group D, indicating an improvement in serum Vitamin D levels. Mild side effects were observed at the end of 4 months.

Conclusion: The present study suggested that Vitamin D as an add-on therapy was found to cause a significant reduction in psoriatic lesions. It could be a promising drug in patients with psoriasis to improve the psoriatic lesions, when combined can reduce the dose of MTX, thereby minimizing the side effects.

Keywords: Moderate chronic plaque psoriasis, Methotrexate, Psoriasis area and severity index, Dermatology life quality index, Psoriasis disability index.

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INTRODUCTION

Psoriasis is a common chronic inflammatory disease consisting of a wide spectrum of clinical phenotypes resulting from an interplay of genetic, environmental, and immunological factors [1]. The prevalence of psoriasis in the world is around 0.1–11.8% and around 0.1–0.3% in Asia [2]. The most common form of psoriasis, chronic plaque psoriasis, affects 80–90% of patients and is characterized by well-demarcated, erythematous plaques overlaid with silvery white scales [3]. Methotrexate (MTX) is an inhibitor of folic acid synthesis and possesses cytostatic and anti-inflammatory properties. It is used for moderate and severe psoriasis as well as psoriatic arthritis. Long-term use of MTX is not recommended due to toxic effects such as myelosuppression, pulmonary fibrosis, hepatotoxicity, etc. [4] Fat-soluble vitamins and their analogs have been considered effective treatments for psoriasis. Deficiencies in these vitamins have been observed in several studies involving psoriasis patients [5]. Recently, the role of Vitamin D in autoimmune skin diseases has been discovered. Vitamin D supplementation has shown to play a beneficial role in psoriatic lesions and resulting in significant improvement in psoriasis area and severity index (PASI) score and improvement in psychological well-being [6]. Vitamin E (alpha-tocopherol) being an established antioxidant gets rid of (reactive oxygen species) which is responsible for a variety of mechanisms leading to skin pathology [5]. The purpose of the study was to evaluate the efficacy and safety of oral Vitamin D_3 and Vitamin E in patients of moderate chronic plaque psoriasis in the Indian population and to compare it with the standard therapy MTX in reducing psoriatic lesions.

METHODS

This prospective, open-labeled, randomized, comparative clinical study was conducted from February 2022 to January 2023 at a tertiary care hospital in Haryana. The study was conducted after obtaining ethical clearance from the Institutional Ethics Committee and written informed consent was taken.

Patients of either sex 20–60 years of age diagnosed as moderate chronic plaque psoriasis with PASI score (3–10) were included in the study while patients with other forms of psoriasis such as guttate, erythrodermic or pustular, with any other autoimmune disease such as SLE or rheumatoid arthritis, receiving any therapeutic intervention which might influence Vitamin D levels, hypersensitivity to study drugs, history of hypercalcemia, nephrolithiasis or parathyroid disease, history of any malignancy such as cutaneous lymphoma or non-melanoma skin cancer, hepatic and renal impairment, history of alcohol intake and smoking, pregnant and lactating women were excluded from the study.

After the screening, 120 eligible patients were randomly allocated into three groups: Group M, Group D, and Group E each having 40 patients. Group M patients received MTX (7.5 mg) tablet orally weekly, Group D patients received MTX (7.5 mg) and Vitamin D_3 (60,000 IU) sachet

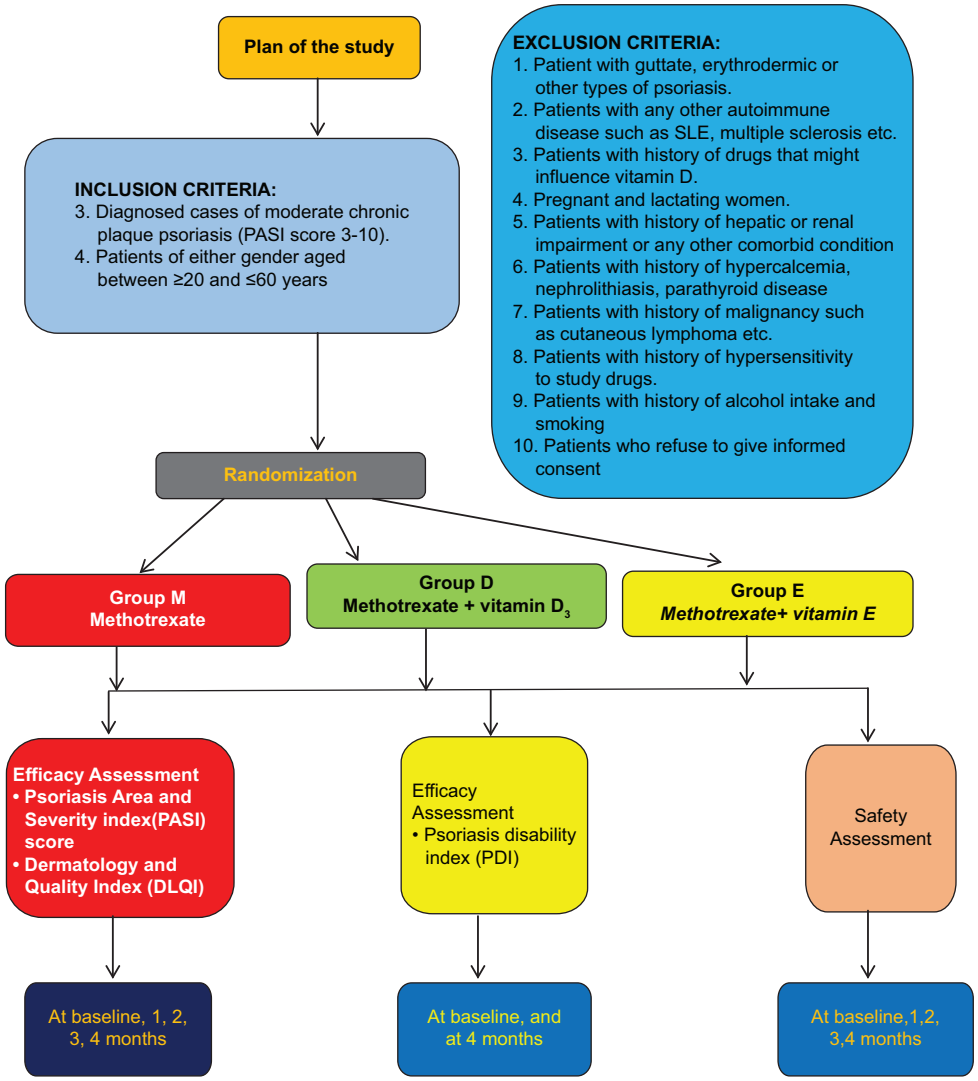

Fig. 1: Flowchart for study

orally weekly, and Group E patients received MTX (7.5 mg) weekly and Vitamin E capsule (400 mg) daily. The medicines were provided to the patients from the hospital supply. All patients received antihistamines (levocetirizine 5 mg) and topical emollients (petroleum jelly, white soft paraffin) daily. Additionally, folic acid 5 mg was administered continuously for 6 days a week, excluding the day when MTX was given. All patients had undergone general physical examination and systemic examination along with relevant investigations such as (complete blood count, random blood sugar, liver function tests, renal function tests, urine complete examination, chest X-rays, electrocardiogram, serum calcium, serum phosphorus, serum Vitamin D (using solid phase competitive ELISA), erythrocyte sedimentation rate, C-reactive protein etc.) at the time of enrolment and 4 months.

Efficacy was evaluated using primary parameters such as PASI, dermatology life quality index (DLQI), and psoriasis disability index (PDI) score and secondary parameters such as Vitamin D deficiency and insufficiency among the study participants and improvement of serum 25(OH)D concentration. PASI and DLQI score was done at baseline, 1 month, 2 months, 3 months, and 4 months. PDI and serum Vitamin D levels were done at baseline and 4 months.

PASI score

The most widely used tool to assess psoriasis severity in clinical trials, PASI reflects not only the body surface area but also erythema, induration, and scaling. The total PASI score ranges from 0 to 72 points. British association of dermatologists define severe psoriasis as a disease with PASI ≥10 and DLQI ≥10, mild as a disease with PASI <3 and moderate as a disease with PASI 3–10 [7].

DLQI

The DLQI is a validated, 10-question, self-reported questionnaire to evaluate the patient's perception of the impact of psoriasis on quality of life. The DLQI questionnaire is divided into 6 commonly identified categories. The DLQI is rated on a 4-point scale (0=not at all to 3=very much). The highest possible total score for the DLQI is 30 and higher scores indicate a more severe impact on quality of life [7].

PDI

The PDI is a 15-item, validated, self-administered questionnaire designed to quantify the functional disability in terms of daily activities, employment, personal relationships, leisure, and treatment effects in adults with psoriasis over the previous 4 weeks. The score ranges from 0 to 45 with higher scores reflecting greater QoL impairment [8].

Safety assessment was carried out at the end of 1 month, 2 months, 3 months, and 4 months for any adverse event and was recorded in the adverse drug monitoring proforma provided by the pharmacovigilance program of India.

Data are expressed as mean±SD. For intragroup and intergroup comparison, *t*-test and analysis of variance were applied. Bonferroni

test was used for normally distributed variables. p<0.05 was considered statistically significant.

RESULTS

A total of 120 patients participated in the study, with 40 patients included in each group, and none of them dropped out during the study. The mean age of the patients in Group M, Group D and Group E were 45.05±16.56, 44.37±15.13, and 44.75±15.44, respectively. The values in all three groups were comparable. The gender distribution is shown in Fig. 2.

In Group M, mean PASI score values at baseline, 1 month, 2 months, 3 months, and 4 months were 6.21±1.91, 5.84±1.85, 5.49±1.84, 5.12±1.84, and 4.72±1.76, respectively. In Group D mean PASI score values at baseline, 1 month, 2 months, 3 months, and 4 months were 6.30±2.19, 5.77±2.01, 5.16±1.89, 4.52±1.85, and 3.92±1.81, respectively. In Group E mean PASI score values were 6.17±1.84, 5.85±1.81, 5.41±1.81, 5.09±1.75, and 4.79±1.74, respectively. On intragroup comparison, in Group M, Group D, and Group E there was a statistically significant reduction in mean PASI score at all follow-up visits as compared to baseline. On intergroup comparison of mean PASI score between Group M, Group D, and Group E statistically significant results were observed at 4 months.

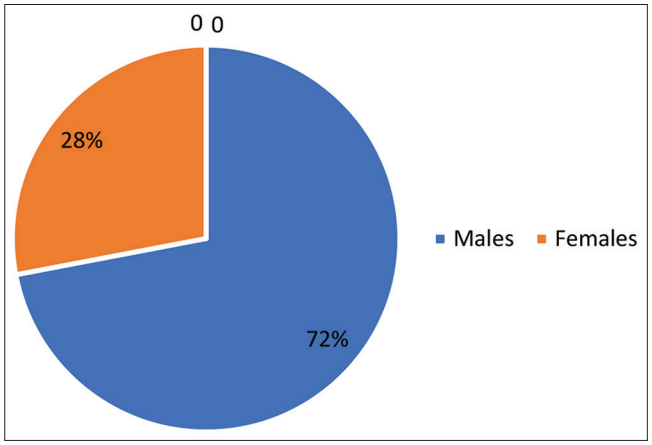

Fig. 2: Pie chart showing gender distribution

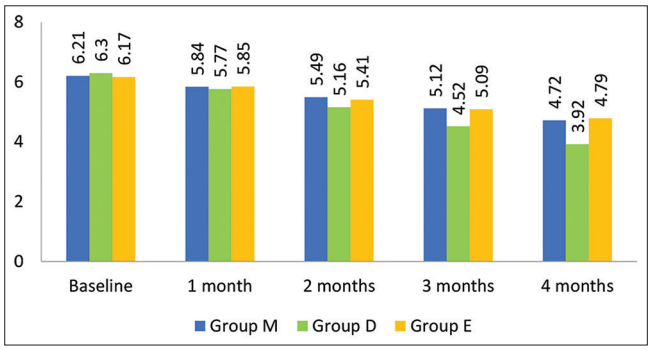

Fig. 3: Bar diagram showing intergroup and intragroup comparison of PASI score

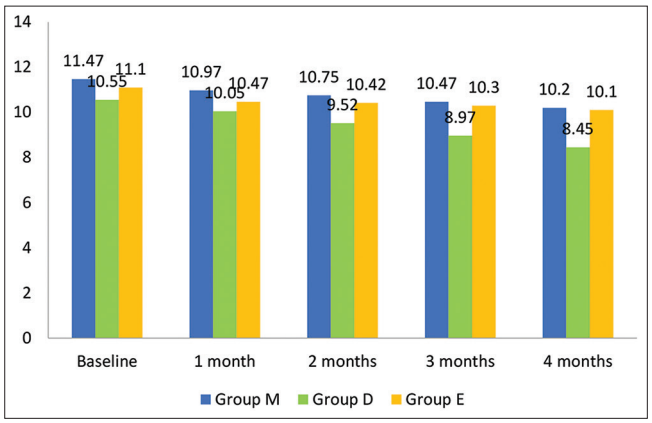

Fig. 4: Bar diagram showing intergroup and intragroup comparison of dermatology life quality index score

In Group M, DLQI score at baseline and the end of 1 month, 2 months, 3 months, and 4 months was 11.47±0.90, 10.97±0.86, 10.75±0.89, 10.47±0.84, and 10.20±0.91, respectively. In Group D, DLQI score at baseline and at the end of 1 month, 2 months, 3 months, and 4 months was 10.55±3.55, 10.05±3.44, 9.52±3.37, 8.97±3.16, and 8.45±3.02, respectively. In Group E, DLQI score at baseline and at the end of 1 month, 2 months, 3 months, and 4 months was 11.1±0.87, 10.47±0.75, 10.42±0.71, 10.3±0.75, and 10.1±0.84, respectively. On intragroup comparison, in Group M, Group D, and Group E there was a statistically significant improvement in mean DLQI score at all follow-up visits as compared to baseline. On intergroup comparison, among all three groups, the mean DLQI score was statistically insignificant at baseline and at 1 month, but it was significant at 2 months, 3 months, and 4 months.

In Group M, PDI values at baseline and 4 months were 20.37±1.21 and 18.52±1.19, respectively. In Group D, PDI values at baseline and 4 months were 18.075±3.26 and 15.42±3.27, respectively.

In Group E, PDI values at baseline and 4 months were 20.07±1.02 and 18.04±1.10, respectively. On intragroup comparison, in Group M, Group D, and Group E there was statistically significant improvement in mean PDI score at follow-up visit as compared to baseline. On intergroup comparison, statistically significant results were found among all three groups at baseline and 4 months.

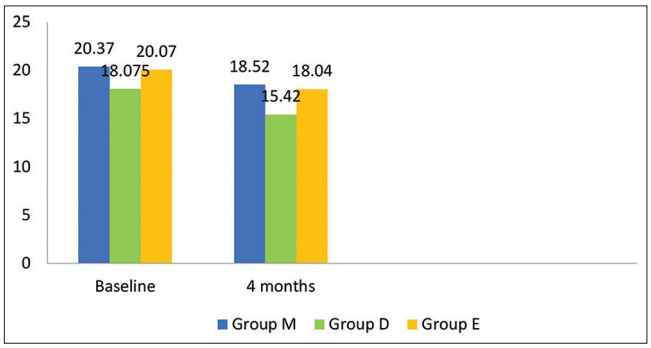

Fig. 5: Bar diagram showing intergroup and intragroup comparison of PDI score

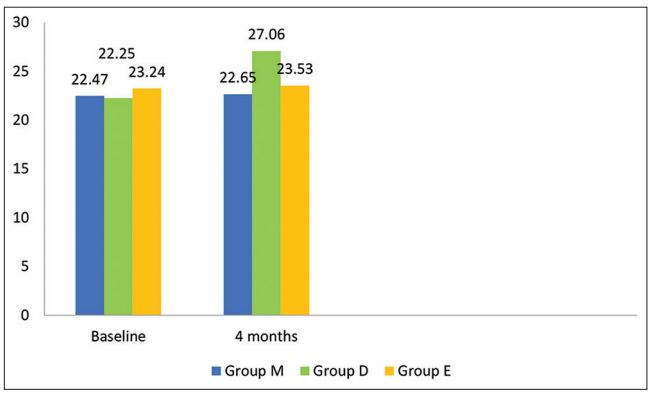

Fig. 6: Bar diagram showing intergroup and intragroup comparison of serum Vitamin D levels

In Group M, serum Vitamin D levels at baseline and 4 months were 22.47±9.46 and 22.65±9.6, respectively. In Group D, serum Vitamin D levels were 22.25±10.13 and 27.06±9.55, respectively. In Group E, serum Vitamin D levels were 23.24±8.6 and 23.53±8.8, respectively. On intragroup comparison, Group M and Group E indicate statistically insignificant improvement in mean serum Vitamin D levels at 4 months when compared to baseline. In Group D, indicates statistically significant improvement in mean serum Vitamin D levels at 4 months when compared to baseline. On intergroup comparison between Group M, Group D, and Group E statistically significant results were observed at 4 months as compared to baseline. At baseline, in Group M, 21 patients were found to be deficient of Vitamin D (<20 ng/mL), and 9 were insufficient (20–30 ng/mL). In Group D 22 were deficient and 9 were insufficient. In Group E 19 were deficient and 14 were insufficient. At 4 months, in Group M, 21 patients were found to be deficient of Vitamin D (<20 ng/mL), and 9 were insufficient (20–30 ng/mL). In Group D 19 were deficient and 10 were insufficient. In Group E 19 were deficient and 14 were insufficient. There was a positive correlation found between serum Vitamin D levels and PASI score.

DISCUSSION

Psoriasis is a chronic, multisystem inflammatory disease that predominately affects skin and joints. Beyond the physical dimensions of disease, there is extensive emotional and psychosocial involvement affecting social functioning and interpersonal relationships [3].

Despite limited evidence, MTX is widely used internationally as an initial therapy in the management of psoriasis and psoriatic arthritis. MTX is approved for use in psoriasis and rheumatoid arthritis but has not been officially approved for psoriatic arthritis in most countries [9]. MTX is a folate antagonist with anti-inflammatory properties. It is used as a first-line treatment for moderate-to-severe psoriasis for more than 50 years [10].

Vitamin D is essential for the maintenance of an intact skin barrier, suppresses inflammatory cytokines such as TNFα, IL6, and IL8, and acts as a mediator in the proliferation of keratinocytes. Topical Vitamin D analogs have long been a part of dermatological treatment of psoriasis but the efficacy of oral Vitamin D remains unclear [11].

Vitamin E is a fat-soluble antioxidant and an important ingredient in cosmetic products. Acting as a free radical scavenger, it protects the skin from deleterious effects. Vitamin E has antitumorigenic and photo-protective properties [12].

In our study, oral Vitamin D_3 and oral Vitamin E with MTX are used and our aim is to reduce the dosage of MTX used and a longer MTX-free and relapse-free interval. De Jong *et al*. recruited 97 patients with psoriasis and the study was divided into 3 phases: (i) A MTX-free phase with double-blind treatment with either calcipotriol ointment or vehicle; (ii) A MTX titration phase with open MTX treatment and additional double-blind treatment with either calcipotriol or vehicle until target response; and (iii) Follow-up phase. Psoriasis was assessed using a modified psoriasis severity score, and patient assessment and safety parameters were observed. It clearly showed that the addition of calcipotriol ointment to MTX treatment resulted in a longer MTX-free and relapse-free interval and cumulative dosages of MTX were lowered as compared with vehicle [13].

In our study, there was significant improvement in PASI score from baseline 6.3 to 3.92 at 4 months and serum Vitamin D levels from baseline 22.25 to 27.06 at 4 months in Group D as compared to Group M and Group E. On intergroup analysis of PASI score, significant results were obtained at the end of 4 months. On intergroup analysis of mean serum Vitamin D levels, statistically significant results were obtained at 4 months. Disphanurat *et al*. also did a double-blind, randomized, placebo-controlled study in which 50 psoriasis patients received Vitamin D2 60,000 IU or similar-looking placebo pills once every 2 weeks for 6 months. PASI score was assessed at 3 and 6 months. At enrolment, the mean PASI score was 4.45, and 26.7% of patients had Vitamin D deficiency. At 3 months, the oral Vitamin D2 group had significantly higher PASI improvement than the placebo group (mean PASI improvement: 1.43 vs. −0.33, p=0.034; mean % PASI improvement: 34.21% vs. −1.85%, p=0.039). The mean serum 25(OH) D level was significantly higher in the oral Vitamin D group than in the placebo group (27.4 vs. 22.4 ng/mL, p=0.029). In our study also there was significant improvement in PASI score and serum Vitamin D levels in Group D as compared to Group M and Group E [14].

Prtina *et al*. conducted a study in which they included 20 adult patients with chronic plaque psoriasis. The patients received Vitamin D capsules in a daily dose of 5,000 IU over 12 weeks. A high dose of Vitamin D supplementation caused a reduction in PASI score in all patients. PASI score decreased from 15.54±10.77 to 8.87±7.38 (<0.001) in all psoriatic patients. In our study, there is the reduction of PASI score from 6.21±1.91 to 4.72±1.76 in Group M, in Group D from 6.30±2.19 to 3.92±1.81 and in Group E from 6.17±1.84 to 4.79±1.74. On intergroup comparison of PASI score, statistically significant results were obtained at 4 months [15].

Hassan *et al*. did a study in which 50 clinically confirmed cases of chronic plaque psoriasis and 50 healthy volunteers were investigated. The mean serum 25 hydroxy Vitamin D levels in psoriatic patients were 22.308±2.974 and in controls were 33.276±2.688. At baseline, the mean serum Vitamin D levels in Group M is 22.47±9.46, in Group D is 22.25±10.13, and in Group E is 23.24±8.6 and at 4 months, the mean serum Vitamin D levels are 22.65±9.6 in Group M, in Group D are 27.06±9.55 and in Group E the serum Vitamin D levels are 23.53±8.8. Statistical significant results were obtained at 4 months. Significant improvement in Vitamin D levels is found in Group D as compared to Group M and Group E [16].

CONCLUSION

Vitamin D_3 combined with MTX resulted in more improvement in PASI score as seen by a significant reduction in PASI score as compared with Group M and Group E. Hence, the addition of Vitamin D_3 to MTX is found to be beneficial in chronic plaque psoriasis, can reduce the dose of MTX, thus minimizing side effects.

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AUTHORS'S CONTRIBUTION

Dr. Garima Narang, Dr. Seema Rani, and Dr. Usha Kataria have all contributed in the development of the protocol, conducting research, data collection, and statistics, and authored the article. Dr. Garima Bhutani and Dr. Rahul Saini have done the editing, statistics, and designing and authored the article.

CONFLICTS OF INTEREST

Nil.

AUTHORS' FUNDING

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