Meta-Analysis of Observational Studies in Epidemiology

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The efficacy and safety of pioglitazone in psoriasis vulgaris

A meta-analysis of randomized controlled trials

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Abstract

Pioglitazone may have potential benefits in the treatment of cutaneous and metabolic derangements of psoriasis, but its role in the treatment of psoriasis remains in debate. We therefore conducted a meta-analysis to evaluate the clinical efficacy and safety of pioglitazone in psoriasis vulgaris (PsV).

We performed a comprehensive search in database of PubMed, Web of Science, Cochrane library, Embase and China National Knowledge Infrastructure (CNKI), and Wan fang database through March 2019 to identify eligible studies. Randomized controlled trials that have evaluated the effect and safety of pioglitazone in PsV were included. Treatment success was defined as ≥75% reduction in psoriasis area and severity index (PASI) score after treatment. Weighted mean differences (WMD), relative risks (RRs) and the corresponding 95% confidence intervals (CIs) were pooled to compare the clinical efficacy and safety between different groups.

Six randomized controlled trials (n = 270) were included. Meta-analysis showed that pioglitazone was associated with a remarkable reduction in PASI score in patients with PsV (weight mean difference: 2.68, 95% CI 1.41–3.94, $P < .001$). The treatment success rate in the pioglitazone group was higher than in the control group (RR 3.60, 95 CI 1.61–8.01, $P < .001$). Compared with control group, pioglitazone was not related to a pronounced increase in total adverse events (RR 1.180, 95 CI 0.85–1.63, $P = .33$). Moreover, the risk of common adverse events in the 2 groups were similar, such as elevated liver enzyme, fatigue, nausea, weight gain.

This meta-analysis suggested pioglitazone is an effective and safe drug in the treatment of patients with PsV.

Abbreviations: CIs = confidence intervals, PPARs = proliferator-activated receptors, PRISMA = Preferred Reporting Items for Systematic Review and Meta-analysis, PsV = psoriasis vulgaris, RRs = relative risks, TZDs = thiazolidinedoniones.

Keywords: pioglitazone, psoriasis vulgaris, meta-analysis

1. Introduction

Psoriasis is a chronic inflammatory skin disease that shares similar pathogenic mechanism with other inflammatory disorders such as metabolic syndrome, insulin resistance and cardiovascular events.[1] The global prevalence of psoriasis is 2% to 3%, which also affects about 0.4% of Asians.[2] Chronic psoriasis vulgaris (PsV) accounts for proximately 90% of the psoriasis cases.[3] Although the pathological process of PsV is unclear, it contributes to the development of various systemic diseases. Also, patients with PsV show high rates of remissions and relapses that require repeated and prolonged of therapy though-out life, resulting in poor quality of life and mental health.[4] Traditional treatments for PsV include methotrexate, acitretin, cyclosporine, and photochemotherapy; however, these drugs have potential

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PFC, XBC, and LL contributed equally to this work.

PubMed, Web of Science, Cochrane library, Embase and China National Knowledge Infrastructure (CNKI), and Wan fang database.

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All data generated or analyzed during this study are included in this published article.

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risks of serious toxi ceffects, such as liver and kidney toxicity, carcinogenesis, and teratogenesis during long-term use, which limits their clinical application.[5,6]

Pioglitazone is a representative of the thiazolidinedoniones (TZDs) drug known in diabetes and dyslipidemia, with no serious side effects in short-term use.[7,8] It works by binding to the proliferator-activated receptors (PPARs) that regulate carbohydrate and lipid metabolism.[9] PPARs are expressed on epidermal keratinocytes, and activation of these receptors have been shown to inhibit the proliferation of psoriatic human keratinocytes in vitro. Some researches reported that TZDs may improve psoriasis by increasing insulin sensitivity and anti-proliferative effects.[10,11] Based on the pro-differentiating and anti-proliferative effects on keratinocytes, pioglitazone may have potential benefits in the treatment of cutaneous and metabolic derangements of psoriasis.[12,13] However, there limited clinical studies focusing on the clinical application of pioglitazone in psoriasis, and their results remain inconsistent. Therefore, we performed a meta-analysis to determine the role of pioglitazone in the treatment of PsV.

2. Materials and methods

2.1. Literature research

The PRISMA protocol was followed in our meta-analysis.[14] We performed a comprehensive search in database of PubMed, Web of Science, Cochrane library, Embase and China National Knowledge Infrastructure (CNKI), and Wan fang database through March 2019 to identify eligible studies, using the search terms as follows: "pioglitazone" OR "thiazolidinedion" OR "TZD" AND "psoriasis." Additionally, manual search of the references in relevant reviews and meta-analyses was performed to find potentially eligible supplements.

2.2. Criteria for inclusion

Studies in patients with PsV were included if they met all of the following conditions:

1. randomized controlled trials with a blind design or not;
2. with a sample size of at least 20 patients;
3. have a clinical follow-up duration >4 weeks;
4. have reported the outcomes we focused on, including psoriasis area and severity index (PASI) scores, therapeutic efficacy, and adverse events;
5. therapeutic efficacy was defined as a reduction in PASI score after treatment ≥75%.

Articles were excluded if they were reviews, comments, abstracts, and duplicates.

2.3. Data collection and quality assessment

Two independent reviewers extracted the details on study and patients characteristics, including the author, year of publication, sample size, age, gender, intervention, observation time, and outcome data. The quality of the included studies was assessed by using the Cochrane collaboration's tool for assessing the risk of bias,[15] which mainly includes six domains: random sequence generation, allocation concealment, binding of participants and personnel, binding of outcomes, incomplete outcome data, and selective reports. Any disagreements between the 2 reviewers were handled by consulting with a third reviewer.

2.4. Statistical methods

We used risk ratios (RRs) and weight mean difference (WMD) and their corresponding 95% confidence intervals (CIs) to report the pooled risk estimates, which were assessed by random effects model. The heterogeneity across studies was examined under Cochrane Q test with a significant value of $P < .1$ and quantified by I^2 statistics, and a value of $I^2 > 50\%$ was considered as significant heterogeneity. A sensitivity analysis was conducted by omitting each study in sequence. Publication bias was detected by using the Egger's test.[16] All statistical analyses were performed using Review Manager 5.2 (RevMan, The Nordic Cochrane Center, The Cochrane Collaboration, 2012) and STATA 11.2 software (Stata Corp, College Station, TX), and P values $< .05$ were considered significant.

2.5. Ethics statement

This study was a secondary analysis of human subject data published in the public domain, thus no ethical approval was needed.

3. Results

3.1. Literature research

The search strategy initially identified 86 publications, of which 29 duplicates and 42 irrelevant studies were removed after scanning the titles and abstracts. The remaining 15 studies were selected for full-text reading, and 9 articles failed to meet the recruitment criteria. Finally, 6 studies[3,9,12,17–19] were included in this meta-analysis (Fig. 1).

3.2. Study characteristics

The main characteristics of the include studies are displayed in Table 1. Briefly, the included studies consist of 270 participants, of which 135 participants were in the pioglitazone group and 135 participants were in the control group. The number of enrolled patients ranged from 16 to 30, with patients' age varying from 18 to 70 years, and male accounted for 68.9% of the total participants. All studies have reported the PASI, and 5 studies have provided the data about treatment success rate, with follow-

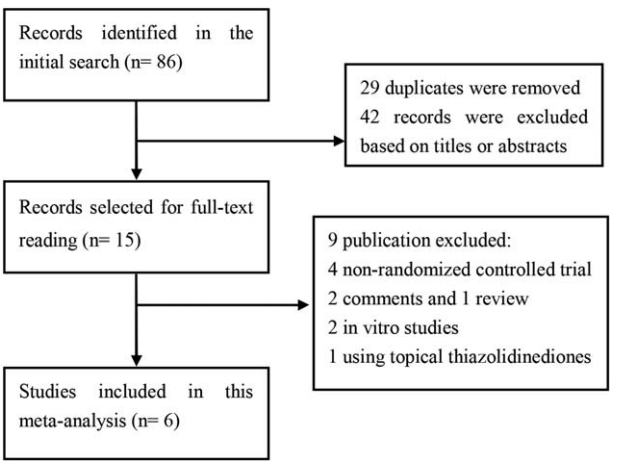

Figure 1. Flow diagram of study search.

Table 1

Baseline characteristics of the included studies.

Study	Patients (n)	Age (years)	Male (%)	Intervention		FU (weeks)
				Experiment	Control	
Ghiasi M 2018	60	43.4	61.6	Pioglitazone (30 mg) + phototherapy	Phototherapy	10
Hafez VG 2015	48	18–5	58.3	Pioglitazone (30 mg)	Placebo	10
Lajevardi V 2015	44	39.3	88.6	Pioglitazone (30 mg) + methotrexate	Methotrexate	16
Mittal R 2009	41	18–65	97.5	Pioglitazone (30 mg) + acitretin	Acitretin + placebo	12
Shafiq N 2005	70	18–70	48.6	Pioglitazone (30 mg)	Placebo	10
Singh S 2016	39	45.4	58.9	Pioglitazone (30 mg)	Placebo	12

up durations ranging from 10 to 16 weeks. None of the included studies showed a high risk of bias according to the Cochrane tool (Supplementary Figure 1, http://links.lww.com/MD/E671).

3.3. Outcome of efficacy meta-analysis

Pooled analyses for change in PASI are displayed in Figure 2. The pooled WMD (95%CI) of PASI change was 2.68 (1.41–3.94) for pioglitazone group vs control group (Fig. 2), with no significant heterogeneity across the studies ($I^2 = 5\%$, $P = .38$). Five studies have reported the treatment success rate, totaling 246 participants. The treatment success rate of was 58.6% (65/111) and 17.4% (21/121), respectively, in the pioglitazone group and control group. The pooled RR (95%CI) of the treatment success event was 3.60 (1.61–8.01) for pioglitazone group vs control group (Fig. 3), with significant heterogeneity across the study ($I^2 = 59\%$, $P = .05$). We performed a subgroup analysis between the pioglitazone only therapy and pioglitazone combined therapy. The outcome of efficacy also showed pioglitazone has a beneficial effect in PsV and pioglitazone combined therapy had more effective than methotrexate, phototherapy or acitretin medicine for PsV (Supplemental Figures 2 and 3, http://links.lww.com/MD/E672 and http://links.lww.com/MD/E673).

3.4. Outcome of safety meta-analysis

The pooled RR (95%CI) of total adverse event was 1.18 (0.85–1.63) for pioglitazone group versus control group (Fig. 4), with no significant heterogeneity across the study (n = 2, $I^2 = 0\%$, $P = .84$). Only 1 study reported[3] a case of myocardial infarction that occurred in the control group, and none of the remaining studies reported any serious adverse events or hypoglycemia events. In addition, the common adverse events in the pioglitazone group and the control group were not significant different, such as elevated liver enzymes (n = 2, $I^2 = 0\%$, $P = .99$; RR 3.06, 95%CI 0.33–28.39), fatigue (n = 2, $I^2 = 0\%$, $P = .48$; RR 0.46, 95%CI 0.12–1.72), nausea (n = 3, $I^2 = 0\%$, $P = 0.92$; RR 0.68, 95%CI 0.20–2.29), weight gain (n = 5, $I^2 = 0\%$, $P = .82$; RR 0.91, 95%CI 0.60–1.37) (Fig. 4).

3.5. Sensitivity analysis and publication bias

Sensitivity analysis by excluding individual study in sequence had no significant influence on the efficacy and safety outcomes. Publication bias was assessed using the data of change in PASI, treatment success event and weight gain. The results showed that there was no evidence of publication bias for these measurements (Egger's test: $P = .65$, $P = .11$, $P = .15$, respectively).

4. Discussion

Our meta-analysis of 6 randomized trials showed that pioglitazone has a beneficial effect in PsV, as shown by the remarkable reduction in PASI score and enhanced treatment success rate. Moreover, the adverse event was not increased compared with the control group. To the best of our knowledge, this is the largest meta-analysis of RCTs using pioglitazone for treatment of PsV. A previous systematical review of 2 studies showed that pioglitazone appears to have efficacy for the treatment of psoriasis.[20] However, their findings were limited by insufficient data and no use of adverse data.

TZDs were the first introduced in the late 1990s, and now are widely used in patients with type 2 diabetes. Recently, nondiabetic effects, such as blood-pressure lowering and fibrinolytic effects, have been demonstrated for TZDs.[21] From a mechanistic view, TZDs are ligands of PPAR-γ that expressed

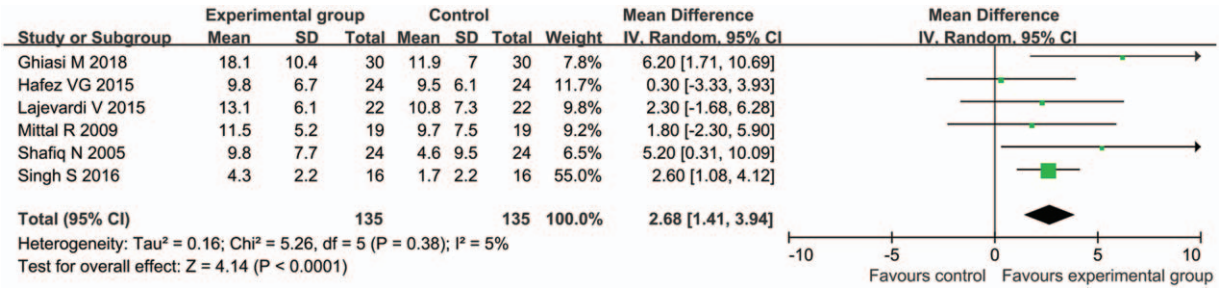

Figure 2. Meta-analyses for change in PASI scores in the pioglitazone trials compared to control group.

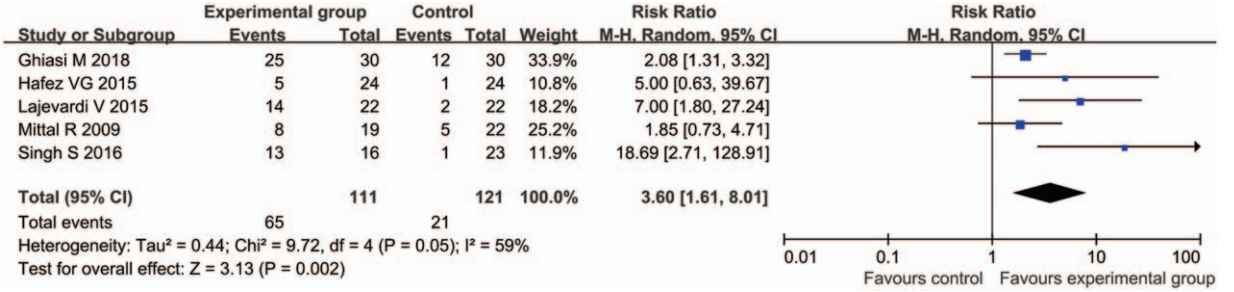

Figure 3. Meta-analyses for the treatment success event in the pioglitazone trials compared to control group.

in many types of cells including epidermal keratinocytes.[11,22] The PPAR-γ agonists regulate anti-inflammatory actions by decreasing the levels of inflammatory cytokines like IL-2, TNF-α, and IFN-γ, and downregulating the expression of adhesion molecules like VCAM-1.[23] IL-17 is the production of T helper type 17 (Th17) cells, Liu et al reported PPAR-γ agonist pioglitazone administration suppressed the production of pro-inflammatory cytokines like IL-17, TNF-α and down-regulated

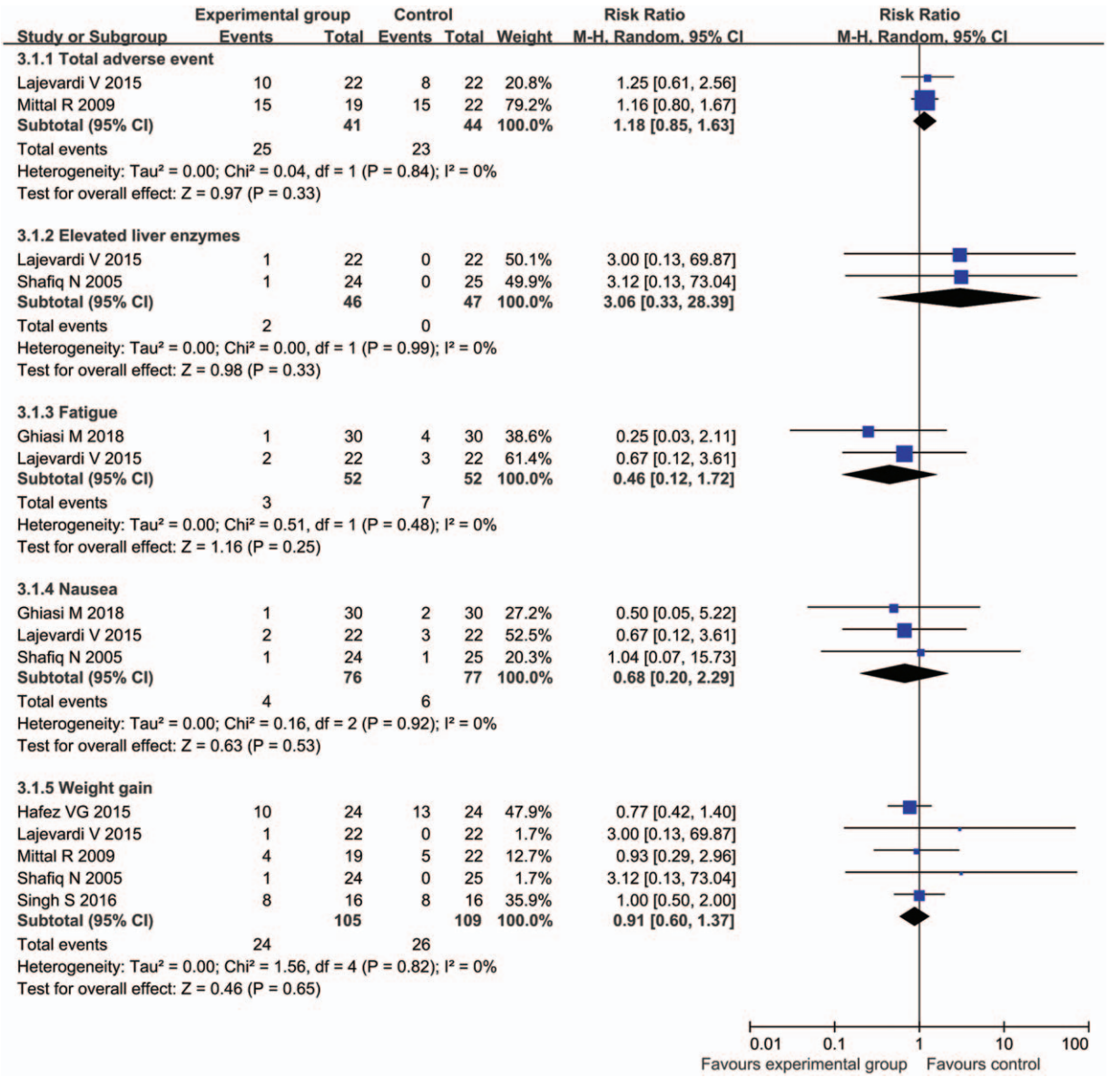

Figure 4. Meta-analyses for the adverse event in the pioglitazone trials compared to control group.

the mRNA expression levels of inflammatory mediators to treat the intervertebral disc degeneration.[24] Disordered cellular including inflammatory cytokines has been indicated in the pathogenesis of psoriasis.[25] PPARs have three members of transcription factors (α, β, γ) that were the nuclear hormone receptors superfamily.[26] These receptors may function important in dermatologic diseases, and the mechanism may be associated with hyperproliferation and aberrant differentiation of the keratinocytes.[27,28] Bhagavathula et al demonstrated rosiglitazone (a potent TZD) inhibited both proliferation and motility as well as elaboration of MMP-1 and MMP-9, thus contributing to the phenotype of psoriatic lesional skin in vitro.[29] Glucocoricoids, vitamin D3, and retinoids play a key role on nuclear hormone receptors with a beneficial effect in the development of antipsoriatic drugs.[19] El-Gharabawy et al reported the activation of PPAR-γ receptors by pioglitazone results in reduced formation of the proinflammatory cytokines and infiltration of the inflammatory cells, indicating the beneficial effects of pioglitazone in treatment of psoriasis.[8] Moreover, our meta-analysis of 6 randomized trials indicated that pioglitazone has a beneficial effect in PsV, as reflected by the improved PASI and treatment success rate. Some studies implied the rosiglitazone was related to an increased risk of cardiovascular death and heart attack, but pioglitazone seems not to share this risk. Therefore, patients and providers should consider the potential of serious adverse cardiovascular effects when using rosiglitazone for type 2 diabetes.[20,30,31] Graham et al have reported that rosiglitazone but not pioglitazone was associated with an increased risk of AMI, stroke, heart failure, or all-cause mortality.[32] TZDs are known to result in elevation liver enzymes, weight gain, fatigue, nausea, and dyslipidemia.[33] However, our meta-analysis did not find any serious adverse events associated with pioglitazone, and pioglitazone did not increase the risk of common adverse events, indicating the safety for the patients with PsV.

There are some limitations in our study. First, all included trials had a small sample size that may result in insufficient statistical power. Secondly, there are some differences in the baseline characteristics of patients, such as disease severity and adjunctive treatment, which may lead to the statistical heterogeneity of the pooling results. Thirdly, the follow-up durations of patients were <4 months; thus, it is unclear that whether pioglitazone could improve the long-term outcomes of psoriasis.

In conclusion, the current meta-analysis of 6 randomized controlled trials totaling 270 participants had revealed that pioglitazone is an effective and safe drug in the treatment of patients with PsV. Further studies with larger sample sizes, longer follow-ups, and diverse populations are needed to confirm our result.

Author Contributions

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Software: Pengfei Chen.
Visualization: Jun Lv.
Writing – original draft: Pengfei Chen.
Writing – review & editing: Jun Lv.

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