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COMPARISONS OF EFFECTIVENESS, SAFETY, AND PHARMACOKINETIC PARAMETERS BETWEEN LOW AND HIGH DOSES OF PIOGLITAZONE IN TYPE 2 DIABETIC PATIENTS

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ABSTRACT

Pioglitazone (PIO) is highly effective in decreasing blood glucose levels for type 2 diabetes mellitus (T2D), but it can induce serious adverse events such as edema and heart failure (HF). Some previous studies showed that the efficacy on glucose control and lipid levels was not related to the difference in doses of PIO in opposite to the incidence of edema which was doses-dependent of PIO**.** To compare glucose control, lipid control, adverse events, and pharmacokinetic (PK) parameters between low and high doses of PIO in T2D. Medical chart of 139 diabetic patients using PIO at Ramathibodi hospital were reviewed to compare outcomes and adverse effects between low and high doses of PIO. 38 patients who stabilized dose of PIO and agree to participate were recruited to collect 2 blood samples at 2 appropriated times and were analyzed their PIO concentrations, then, PK parameters were determined. The outcomes of glucose control and lipid control were not differences between low and high dose of PIO, but edema and HF events were significantly higher in high dose of PIO (P=0.010 and P=0.014, respectively). For PK parameters of PIO, elimination rate constant (k_e) and clearance rate (CL) values of patients who were stabilized on high dose of PIO were significantly higher (P=0.022 and P=0.031, respectively) while elimination half-life ($t_{1/2}$) was significantly shorter (P=0.007) than those who were stabilized on low dose of PIO. PK monitoring for optimal dose of PIO might possibly provide good controlling of blood glucose and lower adverse events in T2D.

Keywords: Pioglitazone, Pharmacokinetics, Effectiveness, Safety and Diabetic patients

INTRODUCTION

Pioglitazone is an oral anti-diabetic agent belonging to the thiazolidinediones (TZD) class of medications. Pioglitazone is potent and highly selective agonists for the nuclear receptor, peroxisome proliferators activated receptor-γ (PPAR-γ) in adipose tissue, pancreatic β-cells, vascular endothelium, heart, skeletal muscle, kidney and macrophages.[1] Through PPAR-γ-mediated effects, pioglitazone improve insulin resistance and also have pleiotropic effects on insulin secretion, lipid and adipose tissue metabolism, body fat distribution, and vascular endothelial function.[2] Previous clinical studies have shown that pioglitazone improves insulin resistance, decreases blood glucose levels, and also improves lipid control in type 2 diabetes mellitus (T2D).[1,3] However, some patients taking pioglitazone monotherapy or combination therapy were suffering from weight gain, peripheral edema, and fluid retention, which can develop into pulmonary edema or heart failure (HF).[4,5] Edema and fluid retention have emerged as the most common and serious side

effect of pioglitazone and has become the most frequent cause of discontinuation of therapy. [6]

A prospective study[7] evaluated the effect of low-dose pioglitazone (7.5 mg/day) on metabolic control and the incidence of edema compared with a standard-dose pioglitazone (15 mg/day) in T2D patients. The incidence of edema was significantly lower in the low-dose group than in the standard dose group (p=0.0014), while the change of glycosylated hemoglobin (HbA_{1c}) and lipid control did not differ significantly between the two groups. The American Heart Association (AHA) and American Diabetes Association (ADA) recommend that if edema occurs and HF is not presented during TZD therapy, the TZD dosage can be reduced and/or diuretics can be added.[8] Norman and Hollenberg[9] mentioned that edema is a dose-dependent effect and reducing the TZD dosage is a viable option.

Although the previous study[7] showed the efficacy on glucose and lipid control was not doses-dependent of pioglitazone while incidence of edema is associated with the doses. There is lacked information about the association between pharmacokinetic (PK) parameters and the doses of pioglitazone. Therefore, this study hypothesized that the pharmacokinetic parameters of pioglitazone in patients who were stabilized on low dose and high dose might be different, if so, the dosage regimen could be optimized, the lower dosage would be consumed more often. Thus the efficacy could be retained while the incidence of edema could be reduced. In this study, pioglitazone dosage of 15 mg/day or lower was defined as low dose while the dosage of 30 mg/day or higher was defined as high dose.

METHODS

Study Design and Subjects

Retrospective study to compare effectiveness and safety between low and high doses of pioglitazone: This part was a randomized retrospective study from reviewing the medical charts of T2D patients who were treated with pioglitazone. Subjects were recruited from the diabetic clinic and the general medicine clinic at Ramathibodi hospital. Inclusion criteria were T2D patients who received pioglitazone alone or as a combination therapy for more than 6 months. Exclusion criteria were patients with 1) inadequate data of with co-morbid diseases, co-medications, or laboratory tests of glucose and lipid controls; 2) received continuous corticosteroid or furosemide; 3) received calcium channel blockers within 1 month before receiving pioglitazone or during pioglitazone treatment and edema occurred; and 4) have at least one of the following diseases: HF, deep vein thrombosis, nephritic syndrome, untreated hypothyroid, ascites, liver dysfunction (aspartate aminotransferase or alanine aminotransferase >3 times upper limit of normal), and renal insufficiency (serum creatinine; SCr >1.5 mg/dl).

Cross-sectional study to compare PK parameters between low and high doses of pioglitazone: This part was a non-randomized cross-sectional study to compare PK parameters between diabetic patients who were stabilized with low and high doses of pioglitazone (Actos®). The subjects consisted of T2D from the diabetic clinic and the general medicine clinic at Ramathibodi hospital. Inclusion criteria were T2D patients who received pioglitazone alone or as a combination therapy for more than 6 months and had taken a stable dose for at least the last 2 visits, and agreed to participate in this part of study and provided written informed consent. Exclusion criteria were the same of the retrospective study.

The study protocol was approved by the Ethical Committee of the Faculty of Medicine, Ramathibodi hospital, Mahidol University, Bangkok, Thailand. The study subjects provided informed consent to participate in the study. Patient's medical information was confidentially protected.

***Pharmacokinetic Assays*:** The total blood samples drawn were 20 ml (10 ml from the first collection and 10 ml from the second collection). The first 10 ml of blood samples were obtained after overnight fasting before taking pioglitazone and were put in a 10 ml of plastic tube containing lithium heparin for investigation of the trough concentration of pioglitazone. The second 10 ml of blood samples were drawn after taking pioglitazone for 4 to 6 hours and were put in a 10 ml of plastic tube containing lithium heparin for further investigation of the peak concentration of pioglitazone. All blood samples were centrifuged at 4°C for 10 minutes at 4,500 rpm, and the serum was transferred into a cryogenic vial and was stored at -80°C until analyzed. The serum pioglitazone concentrations were determined by high-performance liquid chromatography using ultraviolet detector (HPLC-UV), as previously described in study of Sripalakit.[10] Validation of the HPLC method, including linearity, specificity, selectivity, precision, accuracy, and stability, were performed (data not shown).

The PK parameters of pioglitazone in each patient were calculated individually. The PK parameters calculated included the elimination rate constant (k_e),

the volume of distribution (V_d), and the clearance rate (CL), according to the following equations;

$k_e = \ln(C_{max,ss}/C_{min,ss}) / \Delta t$

$V_d = (S)(F)(D)(e^{-k\tau}) / (C_{min,ss})(1-e^{-k\tau})$

$CL = (k_e)(V_d)$

$C_{max,ss}$ = the maximum serum drug concentration at steady state

$C_{min,ss}$ = the minimum serum drug concentration at steady state

Δt = the time interval between $C_{max,ss}$ and $C_{min,ss}$

S = the salt form of a drug; free form is used, S=1

F = the bioavailability factor; drug was assumed to be completely absorbed, F=1

D = the dose administered

τ = tau; the dosing interval

$(1-e^{-k\tau})$ = the fraction of drug that is eliminated within one dosing interval

Statistical Analysis: Demographic data and variables of laboratory test were presented as descriptive statistics, such as frequency, percentage, mean, and standard deviation. Comparisons of gender, co-morbid diseases, co-medication, and adverse events between low and high doses of pioglitazone were analyzed by Chi-square test or Fisher's exact test. The association between pioglitazone doses and edema condition was analyzed by Odds ratio. Comparisons of weight, body mass index (BMI), laboratory tests, and PK parameters between low and high doses of pioglitazone were performed by Student's t test. The difference mean of weight, BMI, and laboratory tests between baseline and after pioglitazone use were analyzed by Paired t-test. All tests were two-tailed, the level of significant was set as P=0.05. Statistical analyses were performed using the SPSS program version 16.0.

RESULTS

Effectiveness and Safety: One hundred and thirty nine patients were included into the retrospective study. Among these, 104 patients belonged to the low dose group (pioglitazone $\leq$15 mg/day), of which 3 patients took 7.5 mg/day and 101 patients took 15 mg/day. There were 35 patients in the high dose group (pioglitazone $\geq$30 mg/day), of which 31 patients took 30 mg/day, 2 patients took 45 mg/day, and the less 2 patients took 60 mg/day. Comparisons of the baseline characteristics between patients treated with low and high doses of pioglitazone (Table I) revealed that there were no significant differences in all variables.

Effectiveness: The effects of pioglitazone were analyzed by comparing the study parameters between baseline and at 6 months in both low and high dose groups (Table II). Nearly all variables assessed showed significant differences between the values at baseline and after pioglitazone had been used for 6 months, except total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) levels. Weight and BMI values were significantly increased, while fasting plasma glucose (FPG), HbA_{1c}, and triglyceride (TG) values were significantly decreased. Therefore, both low and high doses of pioglitazone significantly decreased FPG and HbA_{1c} levels in 6 months. Comparisons of the mean change of weight, glucose control, and lipid control during 6 months between patients used low and high doses of pioglitazone were also revealed in table II. FPG was the only study parameter which showed significant difference between low and high dose groups, the mean FPG of patients in the high dose group decreased in a greater extent than that of the patients in the low dose group.

Safety: Adverse events of pioglitazone were studied in all patients for an average of 3.9 years, which focused on the effects of doses of pioglitazone on edema and HF (Table III). Significant difference in the percentage of edema and HF was found between patients treated with low and high doses of pioglitazone. The risk of edema in patients who were treated with high dose of pioglitazone was significantly higher than the risk in patients who were treated with low dose of pioglitazone (OR=3.38; 95%CI, 1.29 to 8.86). Incidence of edema was recorded in 15.1%. The average duration of pioglitazone used until the incident of edema was 6.1 months (ranged from 0.5 to 14.0 months). 47.6% of the patients with edema (10 of 21 patients) were withdrawn from pioglitazone. The rate of HF in all patients was 3.6% which all were withdrew from pioglitazone. The average duration of pioglitazone used until incident of HF was 0.8 years (ranged from 0.2 to 1.3 years).

Pharmacokinetic Parameters: Thirty eight patients treated with pioglitazone were recruited for pharmacokinetic study. Most patients in high dose group were started with 15 mg/day of pioglitazone, and then the dose was titrated to 30, 45, or 60 mg/day while most patients in low dose group were started and continued with 15 mg/day of pioglitazone. However, the durations of pioglitazone used between the two groups were not significantly different (Table IV). There were no significant differences between the two groups in baseline. Pharmacokinetic parameters between patients treated with low and high doses of pioglitazone were compared. The k_e, $t_{1/2}$, and CL of pioglitazone were significantly

different between the two groups (Table IV). The patients who received low dose of pioglitazone had longer $t_{1/2}$ than the patients who received high dose of pioglitazone, as their k_e and CL were slower.

DISCUSSION

This study confirmed the effectiveness of pioglitazone on glycemic control as there was a significant improvement of HbA_{1c} and FPG levels after 6 months used of both low and high doses of pioglitazone. The average reduction of HbA_{1c} reported in this study was higher than reduction of HbA_{1c} in previous studies,[7,11-14] which might be related to the high percentage of subjects in this study treated with triple therapy. Moreover, this study found that low dose of pioglitazone was as effective as high dose of pioglitazone in reducing HbA_{1c}, which was similar to the results reported by Majima study.[7] Some previous studies[7,11,13-14] had reported that both low and high doses of pioglitazone affected significantly on the reduction of TG from baseline, as also found in this study. However, no significant differences in HDL-C, LDL-C and TC levels were found, which was differed from the results of previous studies in which significant increase in HDL-C and LDL-C levels after pioglitazone use were reported.[11,13-14] Moreover, this study found no difference in mean lipid changes between patients using low and high doses of pioglitazone, while Majima study[7] showed significant difference of HDL-C changes between different doses of pioglitazone. The increase in weight and BMI after 6-month used of pioglitazone in both low and high doses groups in this study was consistent with those previously reported.[7,11,13-14] These previous studies suggested that the increase in average weight appeared to be dose-dependent among patients treated with pioglitazone. However, no difference of weight changes between patients using low and high doses of pioglitazone was observed in this study as might be associated with unidentified confounding factors. This study showed that edema was related to dose of pioglitazone which confirmed the findings in previous studies.[7,11,15] This study identified 15.1% prevalence of edema while other studies reported 5.9-33.0%,[1,16] depending on whether patients received pioglitazone monotherapy or combination therapy and concurrent drugs related to edema. This study also found that HF occurred more often in high dose of pioglitazone than in low dose of pioglitazone that was similar to the reported of Takeda.[17] The results indicated a serious adverse event that could occurred when treated with high dose of pioglitazone. Thus, patients initiated with low dose or high dose of pioglitazone could have similar reduction in HbA_{1c} levels, but patients with low dose of pioglitazone had lower rate of edema and HF comparing with high dose of pioglitazone. The PK results of this study showed that, in high dose group, k_e was higher but the CL, V_d, and V_d/F were lower than the results from the previous study in Thai healthy subjects.[18] The $t_{1/2}$ of high dose of pioglitazone in this study was shorter than the $t_{1/2}$ reported by several previous studies.[18-20] However, the $t_{1/2}$ data in both groups of this study were longer while the CL and Vd/F were lower than those reported of Takeda.[17] The PK study revealed that one of the main reasons for higher dosage requirement in the high dose group was due to the PK variations in individual patient. The patients in the high dose group had faster pioglitazone elimination than those in the low dose group as indicated by a significantly faster in the k_e, much faster in CL and a shorter $t_{1/2}$. Plausible explanations of faster drug elimination might be genetic manifestation, of which might involve CYP2C8 genotypes. A previous study[21] found that patients with CYP2C8*1/*3 or *3/*3 genotype had significantly lower area under the serum concentration-time curve (AUC) and higher CL of pioglitazone than patients with CYP2C8*1/*1 variants (wild type), resulting in shorter $t_{1/2}$ of the drugs. However, since the trough concentrations were not significantly different between the two dosage regimens and the glycemic control was similar, indicating that the efficacy of the reduction of HbA_{1c} might be a time dependent type and not a concentration dependent type since the $C_{max,ss}$ was significantly higher but the efficacy was similar. In contrary, the adverse events of edema and HF might be affected by a higher $C_{max,ss}$. Therefore, a careful monitoring for the PK parameters may assist the determination of the appropriate dosage regimen for individual patients and some unnecessary risks for life threatening side effects might be avoided or at least reduced.

In addition, Takeda[17] reported drug interactions between pioglitazone and CYP2C8 inhibitor, including gemfibrozil and ketoconazole, and indicated that they significantly increased AUC and $t_{1/2}$ of pioglitazone while drug interaction of pioglitazone with CYP2C8 inducer, including rifampicin and atrovastatin, significantly decreased AUC of pioglitazone. Although this study found no significant different in co-medication with gemfibrozil and statins between patients using low and high doses of pioglitazone, we did not monitor the concurrent medication use of ketoconazole and rifampicin. Thus, these drugs might affect the PK parameters found in this study.

This study has several limitations. First, the sample size of the high dose group in the retrospective study was much smaller than the low dose group. This might affect the differences between the two groups in effectiveness and adverse events. Second, in the part of PK study, sample size were also small in both low and high dose groups while a wide standard deviation of PK parameters were found and thus, might affect the interpretation of the results. Third, the subjects of the two parts of this study were not from the same group and were not equal in number with a much smaller number in the part of PK study. Thus, the PK parameters might not be able to represent the effectiveness and the safety of the subjects in the retrospective study. Fourth, we did not analyze the two active metabolites of pioglitazone (M-III and M-IV) which might provide further explanation of the reduction of HbA_{1c} between different dosage groups. Lastly, some drugs with either inducer or inhibitor effect on CYP2C8, which could affect the AUC and $t_{1/2}$ of pioglitazone, were not recorded.

CONCLUSION

The effects of pioglitazone on the average reduction of HbA_{1c} and TG showed no significant difference between low and high doses of pioglitazone. Weight and BMI increased during the first 6 months in both groups, but no significant difference was found. The study results suggested that dose-related adverse events as edema and HF were confirmed. Thus, diabetic patients who responded to low dose of pioglitazone for glycemic control apparently had greater benefits of having lower rate of adverse events, while the change of lipid profile were not significantly difference. Since PK study indicated that at least part of the reasons for higher dosage requirement was due to a faster elimination rate in the high dose group, carefully monitoring for the PK parameters especially for the trough level might be beneficial for patients in clinical setting. However, further studies in a larger patients group are required to confirm the results. Besides, further genetic analyses are also important to identify the types of gene related to the effectiveness and the side effects of this drug.

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Table I. Baseline characteristics of patients treated with low and high doses of pioglitazone

Variable	Low dose[a] (≤15 mg/day) (n=104)	High dose[a] (≥30 mg/day) (n=35)	p-Value
Female sex [n (%)]	72 (69.2)	18 (51.4)	0.057
Age (y)	57.8 [9.9]	59.9 [10.2]	0.272
Weight (kg)	66.4 [11.2]	66.5 [11.3]	0.960
Body mass index (kg/m^2)	26.5 [4.2]	25.6 [3.4]	0.337
Duration of diabetes (years)	9.5 [5.5]	10.5 [5.5]	0.397
FPG (mg/dl)	194.4 [50.9]	195.5 [65.7]	0.914
HbA_{1c} (%)	9.5 [1.5]	9.2 [1.6]	0.426
Serum creatinine (mg/dl)	0.9 [0.3]	1.0 [0.3]	0.094
CL_{CR} (ml/min)	74.0 [25.2]	69.9 [19.2]	0.443
Total cholesterol (mg/dl)	188.2 [36.1]	201.1 [39.9]	0.144
LDL cholesterol (mg/dl)	108.9 [32.5]	111.8 [33.0]	0.681
HDL cholesterol (mg/dl)	43.5 [12.4]	45.3 [14.2]	0.565
Triglycerides (mg/dl)	186.5 [101.7]	217.4 [127.4]	0.265
Patterns of anti-diabetic drugs [n (%)]			
PIO	1 (1.0)	0 (0)	0.748
1 of SU/MET/AGI + PIO	15 (14.4)	6 (17.1)	0.698
2 of SU/MET/AGI + PIO	69 (66.3)	22 (62.9)	0.707
SU + MET + AGI + PIO	6 (5.8)	2 (5.7)	0.676
INS + PIO	1 (1.0)	1 (2.9)	0.442
SU/MET/AGI + INS + PIO	12 (11.5)	4 (11.4)	0.627
Patterns of anti-dyslipidemic drugs [n (%)]			
No drug therapy	17 (16.3)	4 (11.4)	0.482
Statin	72 (69.2)	25 (71.4)	0.807
Fibrate	10 (9.6)	2 (5.7)	0.376
Statin + Fibrate	5 (4.8)	4 (11.4)	0.162

a Values are expressed as mean [SD] unless specified otherwise.

***FPG** = fasting plasma glucose; **HbA_{1c}** = glycosylated hemoglobin; **CL_{CR}** = creatinine clearance; **LDL** = low-density lipoprotein; **HDL** = high-density lipoprotein; **PIO** = pioglitazone; **SU** = sulphonylurea; **MET** = metformin; **AGI** = alpha-glucosidase inhibitor; **INS** = insulin.*

Table II. Effects of low and high doses of pioglitazone on weight, glucose control, and lipid control

Variable	Low dose[a] (≤15 mg/day) (n=104)			High dose[a] (≥30 mg/day) (n=35)		
	Baseline	Month-6	Change	Baseline	Month-6	Change
Weight (kg)	66.4 [11.2]	67.9 [11.0]***	2.2 [2.7]	66.5 [11.3]	68.1 [12.4]***	1.8 [1.8]
BMI (kg/m^2)	26.5 [4.2]	27.1 [4.1]***	0.9 [0.9]	25.6 [3.4]	26.2 [3.7]***	0.6 [0.7]
FPG (mg/dl)	194.4 [50.9]	154.4 [45.6]***	-38.6 [53.7]	195.5 [65.7]	132.3 [34.3]***	-67.9 [57.9]#
HbA_{1c} (%)	9.5 [1.6]	8.2 [1.3]***	-1.3 [1.5]	9.2 [1.6]	7.6 [1.0]***	-1.4 [1.1]
TC (mg/dl)	188.2 [36.1]	181.5 [33.9]	-5.8 [36.0]	201.1 [39.9]	201.6 [35.4]	-4.3 [43.4]
LDL-C (mg/dl)	108.9 [32.5]	111.1 [30.6]	4.3 [33.5]	111.8 [33.0]	112.0 [29.4]	2.8 [27.9]
HDL-C (mg/dl)	43.5 [12.4]	45.2 [14.7]	3.1 [10.7]	45.3 [14.1]	47.4 [18.1]	1.9 [7.4]
TG (mg/dl)	186.5 [101.7]	149.3 [67.2]**	-44.9 [97.1]	217.4 [127.4]	162.7 [97.0]*	-65.0 [123.3]

a Values are expressed as mean [SD].

** p <0.05 vs. baseline; ** p <0.01 vs. baseline; *** p <0.001 vs. baseline*

 # p <0.05 vs. low dose group

***BMI** = body mass index; **FPG** = fasting plasma glucose; **HbA_{1c}** = glycosylated hemoglobin; **TC** = total cholesterol; **LDL-C** = low-density lipoprotein-cholesterol; **HDL-C** = high-density lipoprotein-cholesterol; **TG** = triglycerides*

Table III. Adverse events of low and high doses of pioglitazone

Adverse event	Low dose (≤15 mg/day) (n=104)	High dose (≥30 mg/day) (n=35)	p-Value
Edema [n (%)]	11 (10.6)	10 (28.6)	0.010
Heart failure [n (%)]	1 (1.0)	4 (11.4)	0.014

Table IV. Baseline characteristics and pharmacokinetic parameters of the patients recruited for pharmacokinetic study

Variable	Low dose[a] (≤15 mg/day) (n=17)	High dose[a] (≥30 mg/day) (n=21)	p-Value
Baseline characteristics			
Female sex [n (%)]	14 (82.4)	14 (66.7)	0.237
Age (y)	56.2 [8.1]	55.5 [9.5]	0.811
Weight (kg)	67.6 [15.0]	73.0 [13.6]	0.255
Body mass index (kg/m^2)	27.1 [4.5]	27.7 [3.8]	0.652
Duration of diabetes (years)	8.9 [5.2]	10.0 [3.1]	0.443
Duration of PIO use (years)	4.0 [1.8]	4.7 [1.5]	0.230
HbA_{1c} (%)	8.0 [0.9]	8.2 [1.3]	0.473
Serum creatinine (mg/dl)	1.1 [0.3]	1.1 [0.3]	0.850
Creatinine clearance (ml/min)	67.6 [16.9]	78.3 [29.4]	0.170
PK parameters			
$C_{max,ss}$ (ng/ml)	921.8 [457.0]	1466.3 [723.4]	0.008
$C_{min,ss}$ (ng/ml)	347.3 [314.0]	285.0 [311.6]	0.545
k_e (h^{-1})	0.07 [0.05]	0.11 [0.05]	0.022
$t_{1/2}$ (h)	14.5 [7.7]	8.3 [4.3]	0.007
V_d (L)	23.2 [23.1]	26.2 [26.2]	0.711
V_d/F (L/kg)	0.37 [0.42]	0.38 [0.39]	0.927
CL (L/h)	1.15 [0.82]	1.98 [1.33]	0.031

a Values are expressed as mean [SD] unless specified otherwise.

***PIO** = pioglitazone; **HbA_{1c}** = glycosylated hemoglobin; **$C_{max.ss}$** = the maximum serum drug concentration at steady state; **$C_{min,ss}$** = the minimum serum drug concentration at steady state; **k_e** = elimination rate constant; **$t_{1/2}$** = elimination half-life; **V_d** = volume of distribution; **V_d/F** = apparent volume of distribution; **CL** = clearance rate*

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