Influence of CYP1A1 rs1048943 on Short- and Long-term Outcomes of Non-surgical Periodontal Therapy for Generalised Aggressive Periodontitis

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Objective: *To investigate the influence of CYP1A1 rs1048943 on short- and long-term outcomes of nonsurgical periodontal therapy (NSPT) for generalised aggressive periodontitis (GAgP).*

Methods: *The CYP1A1 rs1048943 polymorphisms of 224 GAgP patients were genotyped by time-of-flight mass spectrometry. A total of 125 patients received NSPT and subsequent follow-up for 3 months. Of the 125 patients, 81 were followed for at least 3 years. Clinical periodontal parameters were collected at baseline and at the follow-up visits. Negative binomial regression was used to analyse the association between the number of teeth lost during the 3-year observation period and CYP1A1 rs1048943 genotypes.*

Results: *The mean probing depth (PD) and percentage of sites with Bleeding Index (BI) ≥ 3 were all significantly greater in CYP1A1 rs1048943 G allele carriers than non-carriers at 3 months and 3 years after treatment ($P < 0.05$). In the PD ≥ 7 mm subgroup, the mean PD was significantly higher in G allele carriers than non-carriers at the 3-year follow-up ($P < 0.05$). The other clinical parameters did not show a similar trend ($P > 0.05$). Furthermore, the changes of percentage of sites with BI ≥ 3 were significantly smaller in G allele carriers than non-carriers at 3 months and 3 years after treatment ($P < 0.05$). GAgP patients with the GG genotype had lost more over the 3-year follow-up period compared with patients with the AA genotype ($P < 0.05$).*

Conclusion: *These data indicated that the CYP1A1 rs1048943 AG/GG genotypes may influence the short- and long-term outcomes of NSPT in GAgP patients.*

Key words: *generalised aggressive periodontitis, rs1048943, tooth loss, treatment outcome*

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Generalised aggressive periodontitis (GAgP) is an infectious disease characterised by severe and rapid alveolar bone destruction that can eventually lead to tooth loss. Although the direct cause of GAgP is bacterial infection, the progression and severity of the disease depend on factors related to the host, genetics and the environment[1-3]. Treatment of GAgP is extremely complex and the outcome is also influenced by many host and environmental factors.

A longitudinal study conducted by Hirschfeld included patients who had received periodontal treatment in the maintenance phase and were followed up for 20 years, and found individual differences in the progression of periodontal disease[4]. Due to the existence of individual differences, it is important to determine the prognosis of periodontitis patients in clinical work. From 1991 to 1999, McGuire undertook four longi-

tudinal observational studies that aimed to analyse whether factors such as periodontal clinical indicators, dental malposition, prognosis and interleukin-1 (IL-1) genotype could predict tooth loss, and found that IL-1 genotype could affect tooth loss[5-8]. Therefore, genetic background is an important factor affecting the prognosis of periodontitis, and may also have a certain degree of influence on the effect of periodontal treatment. However, research on the influence of single nucleotide polymorphisms (SNPs) on nonsurgical periodontal therapy (NSPT) is limited and inconclusive. A study found that although the distribution of matrix metalloproteinase-1 (MMP-1) genotypes did not differ significantly between chronic periodontitis and healthy groups, MMP-1-519G allele carriers had a higher percentage of sites with a clinical attachment level (CAL) of 4 to 6 mm compared with AA genotypes after NSPT ($P < 0.05$)[9]. In another study of the same population, MMP-13-77A/G polymorphism had no obvious influence on NSPT[10]. To the best of the present authors' knowledge, there are still no studies on the influence of SNPs on GAgP in a Chinese population.

CYP1A1 rs048943 is a commonly studied SNP in the CYP1A1 (an important subfamily of cytochrome P450 enzymes) gene. It involves an A to G transition, creating an isoleucine/valine substitution in exon 7[11]. Rs1048943 can alter the level of gene expression, leading to a highly inducible activity of the enzyme[12], and in regard to cancer susceptibility and cardiovascular diseases[13-16]. In our previous study, we found that the G allele of the CYP1A1 rs1048943 gene was associated with increased risk of GAgP and periodontal status in a Chinese population, and statistically significant effects for lipid–gene interactions were found between CYP1A1 rs1048943 and high- and low-density lipoprotein for mean probing depth (PD)[17].

The aim of the present study was to investigate the influence of CYP1A1 rs1048943 on short- and long-term NSPT outcomes.

Materials and methods

Subjects

In our previous study, to investigate the association between GAgP and CYP1A1 rs1048943, 224 Chinese patients with GAgP were enrolled from the Department of Periodontology at Peking University School and Hospital of Stomatology from 2001 to 2015. The control group comprised 139 periodontally healthy volunteers recruited from the staff and students of Peking University School and Hospital of Stomatology. Genomic DNA was extracted from the blood sample of all subjects using a blood DNA mini kit (Watson Biotech, Shanghai, China) and MassARRAY matrix-assisted laser desorption ionisation time-of-flight (MALDI-TOF) mass spectrometry was used to genotype CYP1A1 rs1048943 polymorphism (Sequenom; San Diego, CA, USA).

The diagnosis of subjects was established on the basis of clinical and radiographic criteria proposed by the 1999 International World Workshop for a Classification of Periodontal Diseases and Conditions[18], as given below.

The GAgP group were aged 14 to 36 years with at least six teeth affected with PD ≥ 5 mm and attachment loss (AL) ≥ 3 mm with radiographic evidence of interproximal bone loss and a minimum of 20 teeth remaining. According to the latest classification, all patients had to stage IV/grade C periodontitis[19].

The healthy control group were individuals aged 20 to 36 years with PD ≤ 3 mm or no obvious AL.

All GAgP patients were advised to undergo periodontal treatment; however, only 125 patients received the entire nonsurgical periodontal treatment and subsequent follow-up and were enrolled in the present study. Most of the patients lost to follow-up refused to revisit due to the improvement in their self-reported symptoms.

This study was approved by the ethics committee of Peking University Health Science Centre (NO.0313). All participants provided informed written consent when enrolled in the study.

Periodontal treatment

After clinical, radiographic and blood examinations, 125 AgP patients received full-mouth NSPT. The therapy included instruction in oral hygiene, scaling and root planing under local anaesthesia within 1 month and antibiotics administration (0.2 g metronidazole, three times a day for 1 week and 0.5 g amoxicillin, three times a day for 1 week; if allergic to amoxicillin, 0.25 g azithromycin was administered, twice a day for 3 days)[20]. All patients were treated by two experienced periodontists who were blind to genotype status. After NSPT, a 3-month follow-up appointment was scheduled. For the next 3 years, periodontal supportive treatments were carried out every 6 to 12 months. After 3 years, 87 of the 125 AgP patients were reexamined to assess their clinical periodontal condition.

Clinical assessment

All participants received a full-mouth clinical and radiographic assessment during the first visit, and periodon-

Table 1 PI, PD, percentage of sites with BI ≥ 3 and AL from baseline to 3 years.

Variable		Baseline		3 months			3 years		
rs1048943		Mean	SD	Mean	Δ	SD	Mean	Δ	SD
PI	AA (n = 69)	2.39	0.48	1.38	1.01	0.53	1.34	1.05	0.50
	AG + GG (n = 56)	2.43	0.53	1.44	0.99	0.48	1.55	0.88	0.66
	P value	NS		NS			NS		
PD	AA (n = 69)	4.79	0.82	2.94	1.85	0.51	3.03	1.76	0.58
	AG + GG (n = 56)	4.98	1.08	3.15	1.83	0.63	3.35	1.63	0.75
	P value	NS		< 0.05			< 0.05		
% sites with BI ≥ 3	AA (n = 69)	93.10	11.17	25.69	67.41	23.38	34.48	58.62	29.29
	AG + GG (n = 56)	89.95	19.98	37.86	52.09	27.83	53.32	36.63	32.54
	P value	NS		< 0.01			< 0.01		
AL	AA (n = 69)	4.11	1.10	2.52	1.59	0.98	3.19	0.92	1.39
	AG + GG (n = 56)	4.48	1.34	2.78	1.70	1.09	3.46	1.02	1.45
	P value	NS		NS			NS		

NS, not significant; SD, standard deviation. P value refers to differences between the AA and AG + GG groups.

tal clinical parameters were assessed using a manual periodontal probe by two skilled periodontal specialists: Plaque Index (PI), PD, Bleeding Index (BI)[21] and AL. Clinical periodontal parameters were assessed at six sites around each tooth for the whole mouth, excluding the third molars. At 3 months and 3 years after non-surgical therapy, PLI, PD, BI and AL were reexamined. Tooth loss (TL) was calculated as the difference between the residual tooth number at 3 months and 3 years after NSPT for each patient.

Statistical analysis

The primary outcomes were PD, AL and BI change after NSPT. The secondary outcome was TL after NSPT. All data for continuous variables were tested for normal distribution using a Kolmogorov-Smirnov test. Differences of clinical parameters between CYP1A1 rs1048943 risk allele carriers and non-carriers in GAgP patients were compared using an independent *t* test at baseline, 3 months and 3 years after treatment. Intragroup comparisons were made between baseline, 3 months and 3 years using a two-way ANOVA. The difference in the number of patients with/without TL was analysed using a chi square test. The difference in missing tooth type in different genotype groups was tested using a nonparametric test. $P < 0.05$ was considered statistically significant. The data were analysed using IBM SPSS Statistics 20 (IBM, Armonk, NY, USA).

Results

Effect of CYP1A1 rs1048943 genotypes on clinical short-term outcome of NSPT

A total of 125 patients 48 men, 77 women) with GAgP were enrolled in the present study, with a mean age of 27 years (27.09 ± 4.69). CYP1A1 rs1048943 was genotyped in the previous study conducted by the present authors. The effects of NSPT on the clinical parameters between G allele carriers and non-carriers were analysed. There was no significant difference in age and sex distribution between the two groups. At baseline, all clinical periodontal parameters were similar in G carriers and non-carriers. Three months after NSPT, all periodontal clinical parameters improved in both G allele carriers and non-carriers of CYP1A1 rs1048943 (for all clinical parameters, $P < 0.01$). After periodontal treatment, the mean PD and percentage of sites with BI ≥ 3 were significantly higher in G allele carriers than non-carriers ($P < 0.05$). The other parameters did not show a similar trend. Furthermore, the decrease in the percentage of sites with BI ≥ 3 after treatment was smaller in G allele carriers than non-carriers ($P < 0.05$). These results are displayed in Table 1.

To investigate the effect of CYP1A1 rs1048943 genotypes on clinical parameters of differing severity at site level, sites were divided into 4 to 6 mm and ≥ 7 mm subgroups according to PD and AL. In all PD and AL subgroups, there were no significant differences between G allele carriers and non-carriers at baseline and the 3-month follow-up (Table 2).

Table 2 PD and AL from baseline to 3 years in pockets from 4 to 6 mm and ≥ 7 mm subgroups.

Variable		Baseline		3 months			3 years		
rs1048943		Mean	SD	Mean	Δ	SD	Mean	Δ	SD
PD 4 to 6 mm	AA (n = 69)	4.92	0.20	3.04	1.88	0.52	3.14	1.78	0.66
	AG + GG (n = 56)	4.94	0.27	3.16	1.78	0.49	3.42	1.52	0.77
	P value	NS		NS			NS		
PD ≥ 7 mm	AA (n = 69)	7.59	0.37	3.89	3.70	0.77	3.86	3.73	1.01
	AG + GG (n = 56)	7.59	0.46	4.11	3.48	0.88	4.33	3.26	1.06
	P value	NS		NS			< 0.05		
AL 4 to 6 mm	AA (n = 69)	4.82	0.32	2.72	2.10	0.81	3.39	1.43	1.35
	AG + GG (n = 56)	4.93	0.34	2.97	1.96	0.87	3.71	1.22	1.34
	P value	NS		NS			NS		
AL ≥ 7 mm	AA (n = 69)	7.85	0.61	3.88	3.97	1.32	4.40	3.45	1.74
	AG + GG (n = 56)	7.94	0.70	4.31	3.63	1.39	4.90	3.04	1.58
	P value	NS		NS			NS		

P value refers to differences between the AA and AG + GG groups.

Effect of CYP1A1 rs1048943 genotype on clinical long-term outcome of NSPT

At 3 years after NSPT, 87 out of 125 AgP patients were reexamined to assess their periodontal condition. The long-term clinical outcome of treatment was consistent with the short-term outcome. At baseline, all clinical periodontal parameters were similar in G allele carriers and non-carriers. After 3 years, all periodontal clinical parameters had improved in both G allele carriers and non-carriers compared with baseline (for all clinical parameters, $P < 0.01$). From 3 months to 3 years, all clinical parameters had no statistically significant changes (for all clinical parameters, $P > 0.05$). At the 3-year follow-up, the mean PD and percentage of sites with BI ≥ 3 were significantly higher in G allele carriers than non-carriers ($P < 0.05$). Similar to at 3 months, the decrease in the percentage of sites with BI ≥ 3 was statistically smaller in G allele carriers than non-carriers ($P < 0.05$). There were no statistically significant differences in the mean PI and AL between the two groups at 3 years after treatment ($P > 0.05$). These results are displayed in Table 1.

When sites were divided into 4 to 6 mm and ≥ 7 mm subgroups according to PD and AL, in the PD 4 to 6 mm group and both AL subgroups, there were no significant differences between G allele carriers and non-carriers at the 3-year follow-up. However, in the PD ≥ 7 mm subgroup, the mean PD was significantly higher in G allele carriers than non-carriers ($P < 0.05$). These results are displayed in Table 2.

Effect of CYP1A1 rs1048943 genotype on TL after NSPT

At baseline, 87 AgP patients out of 125 had lost a total of 96 teeth. At 3 months after treatment, a further 35 teeth were extracted due to uncontrolled periodontal inflammation. There was no statistically significant difference in the TL rate in patients with different genotypes.

Over the 3-year observational period, 27 out of 87 AgP patients lost a further 60 teeth in total, all of which were extracted due to severe periodontal destruction or combined periodontal-endodontic lesions. Most of the extracted teeth were incisors and molars which are most vulnerable to aggressive periodontitis. Patients with further tooth loss accounted for 87.50% (7/8) of those with the GG genotype, which was significantly higher than 28.13% (9/32) in the AG group and 23.40% (11/47) in the AA group ($P < 0.01$). The mean TL in patients with the GG genotype was much higher than that in patients with AG and AA genotypes (GG 2.38 ± 2.13; AG 0.66 ± 1.36, AA 0.43 ± 1.00, $P < 0.01$). These results are displayed in Table 3.

Discussion

In the present study, we investigated the influence of CYP1A1 rs1048943 on the short- and long-term outcomes of NSPT. In our previous study, we found that the G allele of the CYP1A1 rs1048943 gene was associated with GAgP (odds ratio [OR] 1.56, 95% confidence interval [CI] 1.01, 2.42) and periodontal status[17]. In the present study, at baseline, there was no significant difference in periodontal clinical parameters between

Table 3 TL in 87 AgP patients distributed by CYP1A1 rs1048943 genotypes over the 3-year observation period.

Variable		AA	AG	GG	*P* value
Patient level		11/47 (23.40%)	9/32 (28.13%)	7/8 (87.50%)	< 0.01
Tooth level		20/1233 (1.62%)	21/860 (2.44%)	19/212 (8.96%)	< 0.01
Mean TL for individual[a]		0.43 ± 0.99	0.66 ± 1.36	2.38 ± 2.13	< 0.01
PD[a]		3.69 ± 0.92	4.26 ± 1.16	4.23 ± 1.26	0.220
Tooth type, number	Incisor	7	4	5	NS
	Canine	1	1	0	
	Premolar	4	5	1	
	Molar	8	11	13	

PD of the extracted teeth was from the data gathered 3 months after treatment.
a, data are presented as mean ± SD.

G allele carriers and non-carriers. At 3 months and 3 years after NSPT, the mean PD and percentage of sites with BI ≥ 3 were significantly higher in G allele carriers than non-carriers, and the decrease in the percentage of sites with BI ≥ 3 was significantly smaller in G allele carriers than non-carriers over the short and long observational periods, meaning that G allele carriers had a worse short- and long-term response to NSPT. It is generally known that the effect of periodontal treatment is greatly influenced by oral hygiene. After being given strict and repeated oral hygiene instruction, all patients' oral hygiene improved and there was no difference in mean PI at any stage between G allele carriers and non-carriers. Considering that all patients were non-smokers and systemically healthy and were treated by two experienced periodontists who were blind to genotype status, CYP1A1 rs1048943 polymorphism is most likely to be the causal factor that influenced the treatment effect.

In addition, patients with further TL accounted for 87.5% of those with the GG genotype, a significantly higher percentage than in the AG and AA groups. The mean TL in patients with the GG genotype was much higher than that in patients with AG and AA genotypes. These results were similar to the study of the effect of IL-1 genotype on TL by McGuire and Nunn[8]. They found that a positive IL-1 genotype increased the risk of TL by 2.7 times and heavy smoking by 2.9 times, and the combined effect of IL-1GP and heavy smoking increased the risk of TL by 7.7 times[8].

The present findings suggest that NSPT has a limited effect on periodontal conditions in CYP1A1-rs1048943 G allele carriers. Although frequent maintenance was carried out over the 3-year observational period, G allele carriers still showed more severe inflammatory conditions (e.g. deeper PD, severe BI and more missing teeth), indicating increased risk of recurrence and development of AgP. Therefore, greater attention should be paid to AgP patients with the CYP1A1-rs1048943 G allele to maintain long-term efficacy.

There was still general bleeding on probing (BOP) and deep pockets after complete NSPT in the present study. The treatment outcome seemed to be poorer than in other studies and the maintenance interval seemed to be far too long. It should be noted that the treatment of aggressive periodontitis is extremely complex and influenced by regional cultural specificities in China, such as poor oral hygiene, low awareness of periodontal treatment and unwillingness to receive surgical therapy and extract hopeless teeth. When patients visit a dentist, the disease has often advanced to a later stage; this was why the subjects recruited in the present study displayed such severe periodontal inflammation and destruction. Combined with poor oral hygiene, this made it difficult to provide better control of periodontal inflammation. Thus, there was still general BOP and deep pockets after complete NSPT. This was also why BI was used instead of BOP to measure bleeding and the Periodontal Risk Assessment for Generalized Aggressive Periodontitis was modified[22]. Based on the aforementioned cultural specificities, the maintenance interval of 6 to 12 months was a gratifying result of the present authors' efforts. A shorter maintenance interval was scarcely possible for such a large number of patients. Indeed, comparing the baseline parameters with the outcome at the 3-month follow-up, the improvement was obvious (PD reduction, 1.70 ± 0.99; percentage of sites with BI ≥ 3 reduction, 47.72 ± 36.42 in all 87 AgP patients), with some changes even greater than in other studies[23]. In addition, the percentage of sites with BI ≥ 3 showed no difference between 3 months and 3 years after treatment in G non-carriers ($P > 0.05$). This may indicate that periodontal inflammation had been controlled to a satisfying level after ruling out the genetic influence.

For some GAgP patients, supportive periodontal treatment alone was not sufficient and surgical therapy was recommended. Patients who accepted surgical treatment were not included in the present study. This was because most GAgP patients who came to our clinic

were in the later stages of disease due to the limitations of nonsurgical treatment and surgical treatment was recommended to them, but many refused due to economic and time factors. Moreover, for patients who accepted periodontal surgery, the types of surgery were different, which could affect the treatment outcome. The type of surgery may be a confounding factor in the study of the effect of genes on periodontal treatment. As a result, we focused on the influence of rs1048943 on NSPT.

The number of missing teeth (0.23 per year) in the supportive therapy was in fact greater than in other studies about NSPT. At baseline, patients did not wish to have any teeth extracted, especially young patients; thus, as many hopeless teeth as possible were retained during the period of active therapy. Through active periodontal treatment, the PD and BI of a few hopeless teeth were improved and mobility decreased. However, most of the hopeless teeth fell out on their own or had to be extracted during the maintenance period. To a great extent, TL that occurred during the maintenance period of this study did not result from disease progression, but rather from previous severe destruction that was unable to be treated.

Conclusion

CYP1A1 rs1048943 gene variation was reported to increase the risk for GAgP in our previous study; in this study, we found that this SNP could also influence patients' short- and long-term response to NSPT. These findings may be useful for identifying individuals at higher risk of GAgP, but also valuable in devising preventive and therapeutic strategies against the development of disease and TL. To date, the relationship between CYP1A1 and periodontitis and the role played by CYP1A1 in the pathogenesis and progression of GAgP remain unclear and need further study.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Dr Xian E WANG participated in the design of the study protocol, the inclusion of subjects, the collection and summary of clinical data and the writing of the manuscript; Drs Wen Li SONG, Li XU and Rui Fang LU were responsible for patient inclusion and clinical data collection; Prof. Huan Xin MENG supervised the study and was responsible for revision of the article.

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