

INTERLEUKIN AS BIOMARKER OF RECURRENT APHTHOUS STOMATITIS (RAS): A SYSTEMATIC LITERATURE REVIEW

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ABSTRACT

This review aimed to describe the interleukins and interleukin gene polymorphisms related to and recommended as a RAS biomarker. Articles were searched through PubMed, ScienceDirect, and Cochrane Library databases, using the keywords of "Interleukin" AND "Recurrent Aphthous Stomatitis". The Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) was used, and the writing of this review refers to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines. A total of 8 articles met the criteria and showed a low risk of bias assessment. The level of IL-2, IL-6, IL-8, and IL-18 in the acute clinical phase of RAS were higher than in the recovery phase, but IL-10 levels showed decreased. IL-2, IL-6, IL-10 gene polymorphisms were found to be more frequent in RAS patients compared to controls, while IL-12 gene polymorphisms were found to be less associated with RAS pathogenesis. Interleukins at the proteomic level that recommended as a pro-inflammatory biomarker are IL-2, IL-6, IL-8, IL-12, and IL-18, while an anti-inflammatory is IL-10. Only IL-2 can be recommended as a biomarker at the genomic level, as other interleukins still require more investigation.

Keywords: Interleukin, Recurrent aphthous stomatitis, Biomarker, Gene polymorphism

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INTRODUCTION

Interleukin (IL) plays a role in the immune system, including oral cavity immunity. These important roles include: the activation, differentiation, proliferation and maturation process, also migration and adhesion of immune cells [1]. Interleukins are both pro-inflammatory and anti-inflammatory, so that the main function of interleukins is to modulate the growth, differentiation, and activation of immune cells during the inflammatory response [1, 2]. Interleukin produced by lymphocytes and other cells such as macrophages, eosinophils, mast cells, endothelial cells, and dendritic cells [2]. The synthesis of IL protein begins by copying the deoxyribonucleic acid (DNA) sequence, which will then be expressed in the nucleus. Furthermore, the transcription process starts with separating hydrogen bonds between the nitrogen bases in DNA by the enzyme helicase, resulting in the genetic code and copied into the ribonucleic acid (RNA) molecules [3, 4]. The genetic code is translated in the ribosomes into polypeptides with specific amino acid sequences, then according to the central dogma can increase or suppress in IL protein expression. Interleukin expression is influenced by changes at the genomic level called gene polymorphisms [1, 3].

Interleukin is a small protein secreted by cells and has a specific effect on the interaction and communication between leukocytes during inflammation [5]. Systematically increased Th1 cytokines and local transcription of Th1 genes production have been reported in patients with Recurrent Aphthous Stomatitis (RAS), which is an inflammatory disease of the oral mucosa [6]. IL-2 and IFN- γ are two cytokines secreted by Th1 cells, which are considered to be pro-inflammatory cytokines. Increased levels of both cytokines have also been reported in a group of patients with RAS [7].

RAS is one of the oral diseases often found in Indonesian society, and is also known as "sore mouth" [8]. The etiology of RAS is still not known with certainty [8-10]. However, one of the predisposing factors is genetic, because it is associated with the discovery of the Single Nucleotide Polymorphism (SNP), and the history of RAS is often found in several members of the same family [11]. Genes with polymorphisms have allele or genotype variations at one or more loci of these genes, with a prevalence of at least 1% in a given population [11, 12]. Gene polymorphisms encoding interleukins associated with RAS in certain populations, can be detected early so

that they can help determine individual risk factors in that population [12].

Another known risk factor for RAS is impaired local immunologic response [7, 9, 13]. Impaired local immune response is mediated by oral mucosal epithelial cells. This causes the accumulation of T lymphocytes and increased production of pro-inflammatory cytokines, thus triggering damage to oral mucosal tissue, in the form of ulcers and causing stomatitis [14]. Cytokines found to be associated with RAS include IL-1 β , INF- γ , and TNF- α [11]. Gene polymorphisms of IL-10 in European and American populations [15], and also IL-1 β in European, American [15], and Brazilian populations [16], have also been reported to be associated with the pathogenesis of RAS. Based on these, interleukins at the proteomic and genomic levels related to RAS are interesting and important to explore.

This recent review aimed to explore interleukins at the proteomic and genomic levels in the RAS patient population, without limiting the interleukin types. So far, this theme has not been found published in scientific journals in the last 10 y. Thus, it is hoped that this review article can become a complement and provide the latest scientific information updates regarding the characteristics and role of IL as a RAS biomarker. Another advantage is that the results of this review can be used as the basis for further research material related to the risk factors, diagnosis, and novel treatment of RAS, as well as for the application in the developing of new drugs or monitor the therapeutic effects.

Method

This systematic review follows the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines, and the research questions were structured using PICO (population, intervention, comparison, and outcome) framework. The population was patients with the diagnosis of RAS; the intervention was the measurement of interleukin levels and examination of interleukin gene polymorphisms; the comparison was healthy control/non-RAS patient, or healing phase when compared with the acute phase of the same subject; and the outcomes were the effects/results of the intervention. The article to be reviewed was searched using the keywords of "Interleukin" AND "Recurrent Aphthous Stomatitis" ("interleukin"[All Fields] OR "interleukins"[All Fields] OR "interleukins"[MeSH Terms] OR "interleukins"[All Fields] OR "interleukin"[All Fields]) AND

("recurrence"[All Fields] OR "recurrence"[MeSH Terms] OR "recurrence"[All Fields] OR "recurrences"[All Fields] OR "recurrences"[All Fields] OR "recurrency"[All Fields] OR "recurrent"[All Fields] OR "recurrently"[All Fields] OR "recurrent"[All Fields]) AND ("stomatitis, aphthous"[MeSH Terms] OR ("stomatitis"[All Fields] AND "aphthous"[All Fields]) OR "aphthous stomatitis"[All Fields] OR ("aphthous"[All Fields] AND "stomatitis"[All Fields])). The digital databases used were PubMed, Science Direct, and Cochrane Library. Additional articles searched were also carried out manually by viewing the list of the article references and would be used if they were relevant to the research question.

The inclusion criteria were articles published in the last ten years (2010-2020), in English, available full paper, and specifically address the topic of interleukins in patients with RAS. The exclusion criteria were articles with case report or meta-analysis design study. The identification and screening process was carried out by ID and NN, while the risk assessment procedure was carried out by ID and ISW independently. There was no difference in the results of the risk assessment of bias between the two raters.

The data extracted from the reviewed articles consists of: the type of IL or gene polymorphism in RAS patients, the total population of RAS and controls, the country where the research is carried out or the origin of the population, sample materials, research methods, results, and conclusions. The reviewed articles were assessed for eligibility using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS), so that articles with low risk of bias and good quality were obtained. RoBANS consisted of six domains: selection of participants, confounding variables, intervention (exposure) measurement, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each assessment item is a question that has an assessment point = 1 for the answer "YES" or "Available", while the scoring point = 0 for the answer "NO" or not available. The total score is the sum of the points from the six questions, so the total points range from 0-6. The assessment criterias were: the risk of bias is high or the quality of the article is low if the total points are between 0 and 2, and the risk of bias is low or the quality of the article is high if the total points are between 3 and 6. All selected articles were then reviewed based on the qualitative analysis or thematic analysis

according to the research objectives. The thematic analysis was carried out by identifying and grouping data from articles based on the similarity of specific themes or characteristics or based on the results or conclusions of each article [17].

RESULTS

Articles identified using keywords, resulted in 93 articles from the PubMed database, 406 articles from the Science Direct, and two articles from the Cochrane Library. The screening process using database filters and inclusion criteria obtained nine articles from the PubMed database, four articles from the Science Direct database, and two articles from the Cochrane Library database so that a total of 15 articles were obtained. Furthermore, nine articles had been excluded because they were not in accordance with the research objectives. Two additional articles were then manually identified from the bibliography of the six previously selected articles. A total of eight articles were obtained at the end of the screening stage, which were then assessed for their eligibility using the risk of bias tools and could be reviewed qualitatively. The following in fig. 1 is a flowchart of searching and selecting articles in this research.

Table 1 shows the characteristics of the researched studies based on the examination of interleukin levels. Two articles showed that the research conducted in India [18, 21], two articles in Turkey [19, 25], three articles in Iran [22-24], and one article in China [20]. The number of research subjects in each article consists of 25 to 184 RAS patients, or 551 patients with RAS diagnoses in total. The control subjects consist of 20 to 150 subjects per article, resulting in a total number of 706 control subjects. This review was conducted on 7 observational study articles and one article with the clinical study design. Four articles studied the interleukin levels in RAS and four articles examined the interleukin gene polymorphisms in RAS.

Table 2 shows the characteristics of the reviewed studies based on the examination of gene polymorphisms through blood samples. The RAS associated gene polymorphisms studies consisted of specific alleles and genotypes of IL-2 [22], IL-12 [23], IL-10 [24], and IL-6 [25], using gene sequencing analysis of polymerase chain reaction (PCR) [22-25]. Meanwhile, table 3 is the results from the risk of bias assessment to determine the quality of the selected articles.

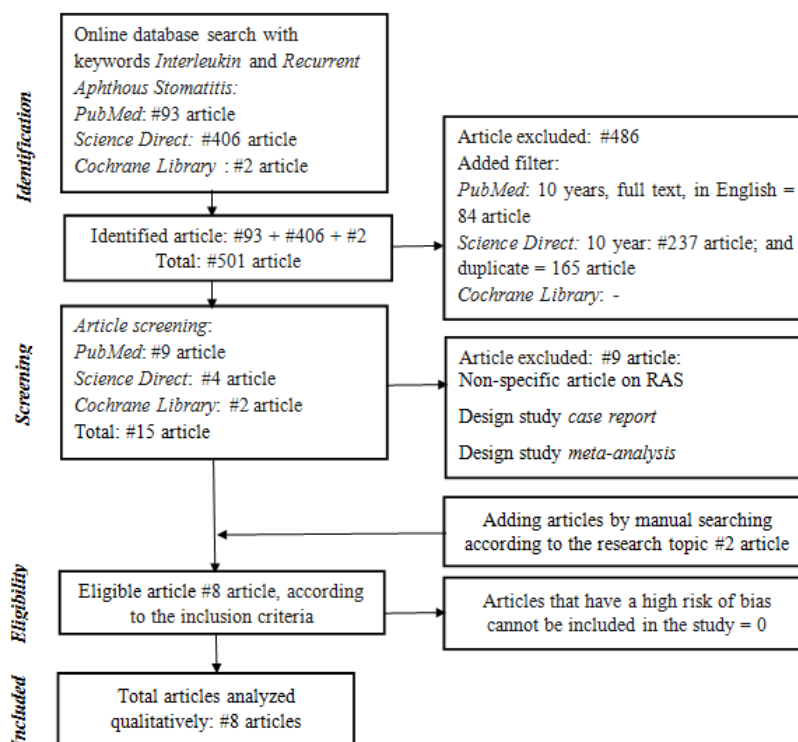


Fig. 1: Flowchart of article search and selection process

Table 1: Characteristics of the reviewed studies based on proteomic level examination

No	Researcher	Aim	Population	Country	Interleukin	Sample	Method	Result	Conclusion
1	Kalpana <i>et al.</i> , 2014 [18]	To measure and compare the salivary IL-2 levels of RAS patients with healthy control, and the variations in age and sex.	60 patients, age of 16-60: - 30 RAS patients (17 females and 13 males) - 30 healthy controls (18 females and 12 males)	India	IL-2	Saliva	Determination of the IL-2 saliva (pg/ml) using the enzyme-linked immunosorbent assay (ELISA) method.	Salivary IL-2 levels were higher in: 1. RAS patients than healthy controls. 2. Patients in the age group of 16-30 y compared to the other age groups. 3. Female than male patients.	IL-2 was a pro-inflammatory interleukin in RAS.
2	Avci <i>et al.</i> , 2014 [19]	To measure and compare the levels of IL-2, IL-10, and IL-12 of the RAS patients and healthy controls.	-25 RAS patients -25 healthy controls (26 females and 24 males at the age of 19-40 y)	Gazi, Turki	IL-2, IL-10, IL-12	Blood	Determination of the levels of IL-2, IL-10, and IL-12 from blood samples using the ELISA method.	1. The levels of IL-2 and IL-12 in the blood of RAS patients were higher than in healthy controls. 2. The levels of IL-10 in the blood of RAS patients were lower than in healthy controls.	IL-2 and IL-12 were pro-inflammatory interleukins, while IL-10 is an anti-inflammatory interleukin in RAS.
3	Lu <i>et al.</i> , 2020 [20]	To measure, compare and determine the relations of plasma IL-6 and IL-18 levels with RAS.	- 60 RAS patients - 60 healthy controls (30 males and 30 females at the age of 25-44 y)	Shanghai Xuhui, China	IL-6 and IL-18	Plasma	Determination of the plasma IL-6 and IL-18 levels (pg/ml), using the ELISA method.	1. The levels of IL-6 and IL-18 in plasma of RAS patients were significantly higher and showed a close relation compared to healthy controls. 2. The levels of IL-6 and IL-18 in the plasma of RAS patients were lower after recovery.	IL-6 and IL-18 were pro-inflammatory interleukins in RAS.
4	Gupta <i>et al.</i> , 2014 [21]	To measure, compare and evaluate the effect of levamisole therapy on IL-8 serum levels in RAS patients compared to healthy controls.	- 20 healthy controls - 30 RAS patients treated with levamisole for 3 mo.	India	IL-8	Serum	Determination of the levels of IL-8 in serum using the enzyme immunoassay IL-8 immunotech method (IM 2237).	1. IL-8 serum levels in RAS patients before levamisole therapy were significantly higher than in healthy controls. (t= 6.53, P<0.001). 2. IL-8 serum levels in RAS patients were significantly reduced by 72% after levamisole therapy compared to before therapy (t = 5.54, P<0.001).	IL-8 was a pro-inflammatory interleukin in RAS and can be inhibited by levamisole.

Table 2: Characteristics of the reviewed studies based on genomic level examination

No	Researcher	Aim	Population	Country	Interleukin	Sample	Method	Result	Conclusion
1	Najafi S <i>et al.</i> , 2017 [22]	To investigate the frequency of IL-2 (G-330 T), (G+166 T) alleles and genotypes in RAS patients compared to healthy controls.	- 64 Iranians with RAS (24 males and 40 females) - 141 healthy controls (101 males and 40 females)	Iran	IL-2	Blood: IL-2 alleles and genotypes	Phenol-chloroform method for isolation of DNA: Gene Sequencing of IL-2 using polymerase chain reaction/sequence-specific	1. IL-2 (+166 G) alleles were lower in RAS patients than in controls. 2. IL-2 (+166 T) alleles were higher in RAS patients than in controls. 3. IL-2 GT genotypes were	Specific Single Nucleotide Polymorphism (SNP) of the IL-2 gene was associated with individual predisposition to RAS in Iranians ethnicity.

No	Researcher	Aim	Population	Country	Interleukin	Sample	Method	Result	Conclusion
2	Moqadam <i>et al.</i> , 2016 [23]	To measure the frequency of IL-12 alleles, genotypes, and haplotypes between RAS patients and the controls group; and the relationship between IL-12 gene polymorphisms in the RAS patients group compared to healthy controls.	- 64 RAS patients - 140 healthy controls	Iran	IL-12	Blood: IL-12 alleles and genotypes	primers (PCR-SSP) assay; Amplification using thermal cycler, Techne Flexigene, and visualization of PCR product with 2% agarose gel electrophoresis; Interpretation using a UV transilluminator and documentation images.	lower in RAS patients than in controls. 4. IL-2 (-330 GT) alleles had no difference between RAS patients and controls. 5. IL-2 GT genotypes were higher in RAS patients than in controls. 6. IL-2 (-330 TT) genotypes were lower in RAS patients than in controls. 1. IL-12 (-1188 A) alleles were higher in RAS patients in controls. 2. IL-12 (-1188 C) alleles were lower in RAS patients than in controls. 3. IL-12 (-1188 AA) genotypes were higher in RAS patients than in controls. 4. IL-12 (-1188 CA) genotypes were lower in RAS patients than in controls. 5. IL-12 (-1188 CC) genotypes were lower in RAS patients than in controls.	<i>Specific Single Nucleotide Polymorphisms</i> (SNPs) of the IL-12 gene were less associated with individual predisposition to RAS in Iranians ethnicity.
3	Najafi <i>et al.</i> , 2014 [24]	To investigate the frequency of IL-10 alleles and genotypes in the RAS patients group compared to the controls group.	- 64 RAS patients (24 males and 40 females), at the average age of 36,6 y - 140 healthy controls	Iran	IL-10	Blood: IL-10 alleles and genotypes		1. IL-10 (T-819) and (A-592) alleles in RAS patients were higher than in controls. 2. IL-10 (GA-1082) genotype in RAS patients was lower than in controls.	<i>Specific Single Nucleotide Polymorphism</i> (SNP) of the IL-10 gene was associated with individual predisposition to RAS in Iranians ethnicity.

Table 2: Characteristics of the reviewed studies based on genomic level examination (continued)

No	Researcher	Aim	Population	Country	Interleukin	Sample	Method	Result	Conclusion
4	Karakus <i>et al.</i> , 2014 [25]	To investigate the polymorphisms relation of IL-6 gene in RAS patients compared to healthy controls in the Turkish	- 184 RAS patients (66 males and 118 females), - 150 healthy controls (62 males and 88 females)	Turkey	IL-6	Blood: IL-6 genotypes	Genomic DNA isolation using commercial DNA isolation kits; IL-6 gene was analyzed using the PCR based on the	1. (-572G>C) genotypes, GG+GC genotypes and G (-572G>C) alleles, (-174G>C) genotypes, and GG	IL-6 gene polymorphisms were found in RAS patients and associated with individual predisposition to RAS in the Turkish population.

No	Researcher	Aim	Population	Country	Interleukin	Sample	Method	Result	Conclusion
		population.					restriction fragment length polymorphism (RFLP); PCR amplification processed using <i>FastDigest BseI</i> and <i>BsrB-I</i> restriction endonuclease.	genotypes and (G-174G≥C) alleles were higher in RAS patients were higher than in controls. 2. The combination of GG-GG genotypes and G-G (-174≥C) haplotypes were higher in RAS patients than in controls.	

Table 3: Risk of bias assessment (RoB)

No	Researcher	Risk assessment of Bias/Item						Total point	Assessment of RoB	Conclusion
		Item 1	Item 2	Item 3	Item 4	Item 5	Item 6			
1	Kalpana <i>et al.</i> , 2014 [18]	1	1	1	0	1	1	5	Low	High quality
2	Avci <i>et al.</i> , 2014 [19]	1	1	1	0	1	1	5	Low	High quality
3	Lu <i>et al.</i> , 2020 [20]	1	1	1	0	1	1	5	Low	High quality
4	Gupta <i>et al.</i> , 2014 [21]	1	1	1	0	1	1	5	Low	High quality
5	Najafi S <i>et al.</i> , 2017 [22]	1	1	1	0	1	1	5	Low	High quality
6	Moqadam <i>et al.</i> , 2016 [23]	0	1	1	0	1	0	3	Low	High quality
7	Najafi <i>et al.</i> , 2014 [24]	1	1	1	0	1	1	5	Low	High quality
8	Karakus <i>et al.</i> , 2014 [25]	1	1	1	0	1	1	5	Low	High quality
Domain Assessment (%)		87,5	100	100	0	100	87,5	-	-	-

Ex: Item 1 = Selection of participants; Item 2 = Confounding variables; 3 = Intervention (exposure) measurement; Item 4 = Blinding of outcome assessment; Item 5 = Incomplete outcome data; Item 6 = Selective outcome reporting; 1 = Yes/available; 0 = No/not available; Total point 0-2 = High risk of bias; Total point 3-6 = Low risk of bias.

The results of the risk assessment of bias for the eight articles mentioned above show that all articles had a low risk of bias assessment and had good quality. Domain *selection of participants* (item 1) and *selective outcome reporting* (item 6) had a percentage score of 87.5%, and this score was considered good because only one of the eight articles in the two domains did not fulfil the criteria. The *Confounding variables* domain (item 2), *intervention (exposure) measurement* domain (item 3), and *incomplete outcome data* domain (item 5) had a percentage score of 100%, and this score was very good because all articles met the expected criteria. All research subjects had followed the research procedure flow and completed it. The worst percentage score was in the domain of *blinding of outcome assessment* (item 4), which is 0% because the entire article did not mention the blinding method in the research procedure. It may be because 7 out of 8 articles were observational studies based on objective assessments, both interleukin levels, and gene polymorphisms, not clinical trial studies that assess subjectively, so they were often not blinded.

DISCUSSION

Tables 1 and 2 show that the research was conducted on populations in Iran, Turkey, India, and China which are part of the West, South, and East Asian continent. Previously published articles show that research on RAS-related interleukins has been carried out in European (United Kingdom, Italy, and Finland) and American populations including Brazilian [15-17], so our review is a complement to the existing scientific information.

Studies on interleukins as biomarkers associated with RAS consist of studies at the proteomic [18-21] and genomic levels [22-25]. A total of three articles researched IL-2 [18, 19, 22]; two articles researched IL-12 [19, 23]; two articles researched IL-10 [19, 24], two articles researched IL-6 [20, 25], one article researched IL-8 [21], and one

article researched IL-18 [20]. Overall, this review results showed that interleukins and IL gene polymorphisms play a role in the pathogenesis of RAS and showed a positive correlation.

There were various sample materials used. Saliva [18], is the most accessible and non-invasive sampling method. Saliva generally reflects blood peptide concentrations and plays a crucial role in oral health to maintain the integrity of the oral mucous membranes through liquefaction and repair of soft tissues [26], so that IL products can be detected in saliva. Interleukins are more systematically distributed in the blood circulation [19-25], but blood sampling is a more invasive procedure than saliva sampling. Blood samples are also used for gene polymorphism examination using the polymerase chain reaction (PCR) method [22-25]. This PCR method can multiply specific DNA up to millions of copies *in vitro*, and can be analyzed more clearly with more specific and accurate results, particularly in detecting the specific alleles and genotypes encoding the IL productions [27].

IL-2 levels had been examined using saliva [18] and blood [19, 22] samples. The examination results obtained that salivary and blood IL-2 levels in RAS patients were higher than in healthy controls [18, 19]. IL-2 levels in patients aged 16-30 y were higher than in other age groups, and IL-2 levels in female patients were also higher than in males [18]. This is in line with the previous studies, that RAS usually began in the second decade of human life and was dominated by women in adult and pediatric patient groups [9]. Likewise, this is also in line with the study of RAS patients in India [26] and with burning mouth syndrome (BMS) patients in Croatia [28]. It implies that IL-2 is a biological marker that increases in active local oral mucosal inflammation, such as RAS and BMS.

IL-2 gene polymorphisms were also examined to determine the frequency of the IL-2 alleles and genotypes in RAS patients. Several

significant differences in alleles, genotypes, and haplotypes were found between RAS patients and controls. The G to T exchange at position+166 of the IL-2 gene allows for increased IL-2 secretion [29]. These results align with other studies conducted in the Chinese population, in which IL-2 gene polymorphisms were associated with individual susceptibility to RAS [30]. The results of this review [22] and the two findings [29, 30], reinforce the recommendation that IL-2 can be used as a biomarker for diagnosis and determining risk factors for RAS.

IL-6 levels in the plasma of RAS patients showed a higher result than in healthy controls [20], and it aligns with the study in the atopic patient group with RAS [27]. IL-6 gene polymorphisms (-174G-C) and (-572G-C) were examined, and obtained results that these polymorphisms affect the formation and course of RAS [25]. Another study of IL-6 gene polymorphisms in the Iranian [31] and the DNA methylation of IL-6 in RAS patients with hematinic deficient and atopy in the Indonesian [32] population, also stated in a similar way, that IL-6 played a role in the pathogenesis of RAS, but inconsistent with a study conducted in the Brazilian population, that found no difference in alleles and genotypes frequencies of the IL-6 gene polymorphism (-174G-C) compared to controls [6]. Based on the data, IL-6 has good potential as a biomarker that plays a role in the pathogenesis of RAS in the proteomic level, however, the IL-6 gene polymorphisms and their relationship to RAS still require further investigation because there are still differences in the research results.

Examination of serum IL-8 levels was carried out to determine the effect of levamisole therapy in RAS patients. Serum IL-8 levels in RAS patients were significantly higher than in healthy controls before levamisole therapy, then IL-8 levels were reduced by 72% after levamisole therapy [21]. These results align with studies on other inflammatory diseases, which stated that IL-8 levels were higher in patients with Pyostomatitis vegetans [33]. So far, there have been no other studies examining IL-8 gene polymorphisms related to RAS.

Examination of IL-10 levels were found lower than in healthy controls [19], so this proves that IL-10 is an anti-inflammatory cytokine in RAS patients. The frequency of IL-10 alleles and genotypes had also been examined. It showed that the SNP of the IL-10 gene was associated with an individual's predisposition to RAS. IL-10 gene polymorphisms at positions 1082(C/A), 819(C/T), and 592(C/A) were investigated and significantly higher in RAS patients compared to controls [24]. The results of this study are different from the previous study, which stated that the IL-10 genotype at position 1082(G/A) of the RAS patient group was not higher than that of healthy controls [6]. These differences can be attributed to differences in population heterogeneity [32], so the IL-10 gene polymorphism in RAS patients still needs further research.

The levels of IL-12 in the blood of RAS patients were higher than in healthy controls [19]. However, the frequency of IL-12 (A-188 C) alleles and genotypes in RAS and control patients of Iranians ethnicity, showed no significant differences. The lack of association between IL-12 polymorphism and RAS may indicate that IL-12 genomically does not have a significant role in the pathogenesis of RAS, but at the proteomic level, it can still be considered as a biomarker in RAS. Another previous study examined the IL-12A and IL-12B alleles and genotypes, stating that gene polymorphisms of IL-12 were associated with individual susceptibility to RAS [30]. Because there are still differences, IL-12 cannot be recommended as a biomarker for RAS.

IL-18 levels had been examined and stated to be related to the pathogenicity of RAS because it was detected to be higher in RAS patients than in controls [20]. It aligns with another study that measured the relationship between IL-18 and psoriasis as an inflammatory disease. The pro-inflammatory activity of IL-18 has been observed in various cells and in various diseases. The imbalance of IL-18 levels can cause inflammation and various diseases [34]. IL-8 can be said to have potential as a biomarker at the proteomic level in RAS as an inflammatory disease, but there has not been adequate research data at the genomic level.

Based on the results of this review, it can be seen that several interleukins play a role in the pathogenesis of RAS, both at the proteomic and genomic levels. The authors can recommend that IL-2, IL-6, IL-8, IL-10, IL-12, IL-18 at the proteomic level and IL-2 at the

genomic level can be used as biomarkers of RAS, because several other studies had shown similar results which is in line with the results of our study. At the genomic level, for now, we only recommend IL-2 as a biomarker of RAS predisposing factors because several studies results had supported it, whilst IL-6, IL-10, and IL-12 still require further investigation.

The limitation of this review is the possibility that there are articles that are in accordance with the research objectives but cannot be identified in the database used, or the full paper is not available. Meanwhile, this review article can become an important information as the basis for further research in the field of oral medicine, related to oral inflammatory diseases (including RAS), and also in the pharmaceutical field related to specific targets in the development of anti-inflammatory drugs.

CONCLUSION

Interleukins that are recommended as a pro-inflammatory biomarker are IL-2, IL-6, IL-8, IL-12, and IL-18, while as an anti-inflammatory is IL-10, at the proteomic level. Only IL-2 can be recommended as a biomarker at the genomic level, as other interleukins still require more investigations.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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