• Investigation •

Incidence, prevalence, and demographic characteristics of ocular cicatricial pemphigoid in Colombia: data from the National Health Registry 2009-2019

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Abstract

● **AIM:** To provide an epidemiological characterization of ocular cicatricial pemphigoid (OCP) in Colombia.

● **METHODS:** We conducted a cross-sectional study using SISPRO. We applied the specific code of the International Classification of Diseases for Ocular Pemphigoid, from 2009-2019 to estimate prevalence, incidence, and the demographic status of the disease in Colombia.

● **RESULTS:** The estimated average prevalence was 0.22 per 1 000 000 inhabitants, and the estimated average incidence was 0.24 per 1 000 000 inhabitants. With a female predominance of 62.5%, and a male/female ratio of 1:1.6. The group of patients diagnosed with the disease after the age of 80 presented the highest prevalence. The departments with the highest prevalence were Antioquia, Bogotá, and Santander.

● **CONCLUSION:** There are important differences between worldwide and Colombian prevalence and incidence data, which may be related to genetic and epigenetic factors, and the possible underdiagnosis of the disease. According to the results, OCP is an extremely rare disease in Colombia. Nevertheless, it is important to encourage awareness of the disease due to its devastating consequences.

● **KEYWORDS:** ocular cicatricial pemphigoid; epidemiology; incidence ophthalmology; Colombia; autoimmune diseases

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INTRODUCTION

Mucous membrane pemphigoid (MMP) is a chronic autoimmune systemic disease that not only affects ocular tissue, but also oral, nasopharynx, tracheal and urogenital mucosa. Nevertheless, 60%-70% of the events correspond to ocular manifestations, known as ocular cicatricial pemphigoid (OCP)[1-2].

OCP is typically presented as a chronic conjunctivitis, characterized by recurrent acute episodes of conjunctival inflammation[3]. It has a very variable natural history, being more accelerated and progressive in some patients and slower in others[4-5]. Studies have shown that 26% of the patients will have visual impairment, while 21% of them will have bilateral blindness[6]. Early detection and initiation of treatment are factors that influence disease progression[6-8].

OCP is a quite rare disease with an estimated incidence of 1 in 20 000 to 1 in 46 000 ophthalmic cases[3,9-10]. Although its incidence varies between worldwide publications there is a lack of epidemiological data of OCP in South American countries[11-12]. Therefore, the aim of this study is to provide an epidemiological description of OCP in Colombia based on the Ministry of Health and Social Protection databases. To the best of our knowledge, this is the first study that describes epidemiological features of OCP in a Latin American country.

SUBJECTS AND METHODS

Ethical Approval This study adheres to the ethical principles for human research established by the Helsinki Declaration, the Belmont Report and Colombian Resolution 008430 of 1993. Concerning the tests classifications, according to the risks that are contemplated in the resolution 8430 from 1993,

this investigation is considered a procedure without risks. The information in the databases used in this article is freely accessible and is available for research purposes. In the same way, their coding system ensures data confidentiality.

Design We conducted an observational descriptive cross-sectional study, based on the STROBE guidelines, in patients diagnosed with OCP, with no age limit, in Colombia.

Population The information and data in this study were obtained from the dynamic tables of the Integral System of Information of Social Protection (SISPRO, by its Spanish acronym), a unique official database of the Colombian Ministry of Health and Social Protection, from Jan. 1, 2009 to Dec. 31, 2019. Baseline demographic population from the National Administrative Department of Statistics (DANE)[13] retroprojections of the last national census of 2018, was considered.

Data Collection For the epidemiological description we used SISPRO[14] in which clinical and demographic data is grouped in the individual records of health service provision (RIPS). This database codifies diseases by the International Statistical Classification of Diseases and Related Health Problems. Thus, we conducted a search for reports of the code H13.3 (ocular pemphigoid).

In order to delimit the results, a first filter by year (2009 to 2019) and type of diagnosis (confirmed new or confirmed repeated) was performed. In order to describe the demographic status of the disease in the country, additional filters, such as area of residence, simple and quinquennial age groups, and sex, were added.

Statistical Analysis We estimated the prevalence and incidence per million inhabitants over a period of 11y. The incidence was calculated using the sum of the total number of new diagnosis per year divided by the total patients who consulted the national health service year by year registered in SISPRO[14], per million inhabitants. For the prevalence, the total number of patients with H13.3, over 2018 retroprojection of DANE was calculated[13], per million inhabitants. We applied these calculations to the filters of age and sex, respectively. For the demographic description, georeferencing maps were made by 5y, 6y, and for the total geographic distribution of the disease.

Bias Control In this study, selection biases may occur due to the large number of filters that can be applied to diagnostic data in RIPS tool. In order to prevent this and to avoid misclassification bias, we only included patients who had a new diagnosis and confirmed repeated diagnosis. This confers security to perform the epidemiological description of this work.

RESULTS

In eleven years, 112 patients had been diagnosed with ocular pemphigoid. The estimated average prevalence was 0.22 per million inhabitants and the estimated average incidence was 0.24 per million inhabitants (Figure 1). More detailed information about epidemiological description is found in Table 1. Females represent 62.5% of the cases with a male-female ratio of 1:1.6 respectively (Table 2). The group of patients diagnosed with the disease after the age of 80 presented the highest prevalence (Figure 2).

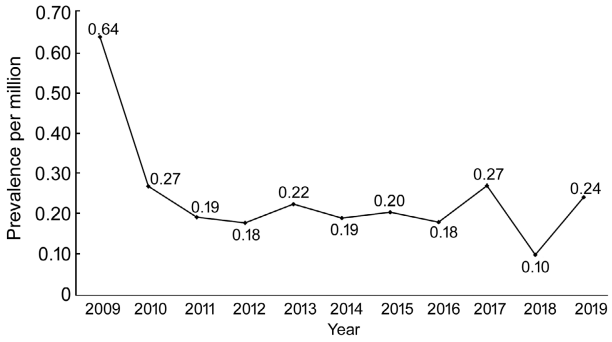

Figure 1 Annual incidence unadjusted of OCP per million from 2009 to 2019 Incidence: (New cases per year / SISPRO consulting population per year) ×1 000 000 inhabitants.

Regarding the demographic distribution of OCP, we observed that the highest number of cases was reported in Antioquia (23.2%), followed by Bogotá (17.8%), Santander (8%), and Valle del Cauca (7.1%). On the other hand, the number of OCP cases has been increasing in the departments of the Colombian coffee zone, such as Antioquia and Caldas, as shown in Figure 3.

DISCUSSION

OCP is a rare condition that causes an important morbidity. Its incidence varies worldwide among publications, from 1/8000 to 1/60 000[10,15-17]. In addition, in Colombia, as in other South American countries, there is a lack of OCP epidemiological data. To the best of our knowledge, this is the first study that describes OCP epidemiological features in a Latin American country.

Comparing our results with the ones reported in the literature, it is important to note that Colombian incidence is much lower than the ones reported in the United States 1/8000-60 000 inhabitants[10,15-17] and the United Kingdom 0.8/1 000 000 inhabitants[18]. Worldwide incidences are shown in Table 3. The incidence difference can be attributed to several causes, ranging from genetic and epigenetics factors to sub diagnosis and limitations of the data bases. These limitations are evident in Figure 1, where a peak is observed in 2009. This could be explained by the compulsory nature of the registration for public and private entities in the country, established in the same year. In the following years it is clear how the incidence trend is maintained.

As it is a rare, insidious, and chronic disease, reported data could be affected because of the requirement of a long time to reach the diagnosis. In a Brazilian study regarding 82 patients

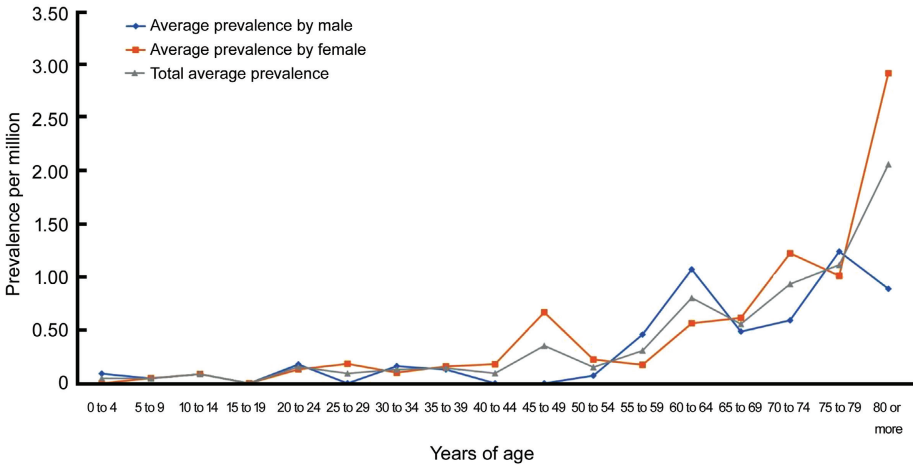

Figure 2 Gender unadjusted average prevalence over quinquennial age of patients with OCP during 2015 to 2019 Prevalence: (Total cases by sex and quinquennial age per year / DANE baseline retroprojections by sex and quinquennial age per year) ×1 000 000 inhabitants.

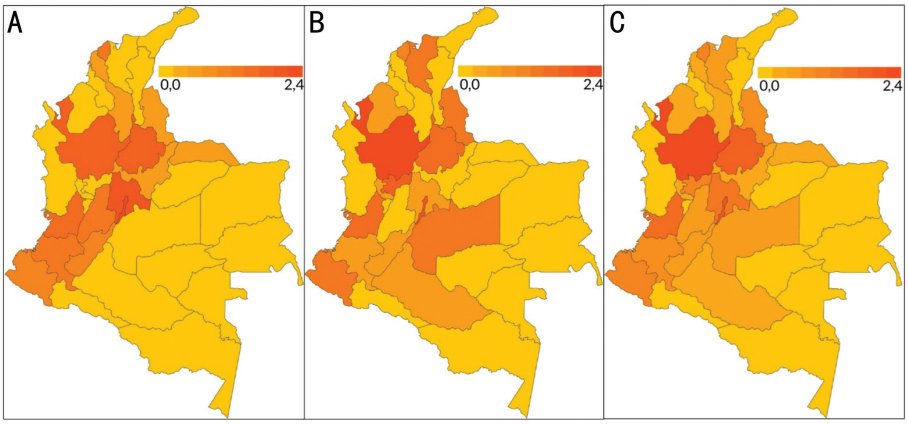

Figure 3 Colombian average distribution of OCP by departments A: Distribution of 2009 to 2013; B: Distribution of 2014 to 2019; C: Distribution of 2009 to 2019. Antioquia and Colombian coffee zone prevalence has been increasing throughout the years, as it is evident in this figure; A shows these zones in a lighter color, while B shows a stronger color; C shows the mean prevalence by department throughout the years studied in this article.

Table 1 Epidemiological description of patient with OCP as primary diagnosis in Colombia per year

Year	Consulted patients (SISPRO)	New confirmed diagnosis	Incidence	Colombian population (DANE)	Total cases	Prevalence
2009	17 314 625	11	0.64	43 884 616	15	0.34
2010	18 637 549	5	0.27	44 349 775	6	0.14
2011	20 798 465	4	0.19	44 796 093	7	0.16
2012	22 421 907	4	0.18	45 217 714	9	0.20
2013	22 275 123	5	0.22	45 622 930	7	0.15
2014	26 298 070	5	0.19	46 021 270	9	0.20
2015	24 454 582	5	0.20	46 431 100	8	0.17
2016	22 217 056	4	0.18	46 900 058	9	0.19
2017	25 959 380	7	0.27	47 407 570	13	0.27
2018	30 078 667	3	0.10	48 258 494	12	0.25
2019	33 136 903	8	0.24	49 395 678	17	0.34
Average	NA	6±2.296	0.24	NA	10±3.573	0.22

Table 2 OCP reported incidence worldwide

Country	Year	Author	Incidence
USA	1934	Smith *et al*[10]	1 in 46 000 patients/y
	1942	Lever *et al*[15]	1 in 12 000 to 1 in 60 000 patients/y
	1964	Bedell[16]	1 in 8000 patients/y
	1972	Bettelheim *et al*[17]	1 in 15 000 patients/y
UK	2012	Radford *et al*[18]	0.8 patients/ million/ y

with oral manifestations of dermatologic systemic diseases, a prevalence of 7.3% of MMP was found[19]. To the best of our knowledge, there are only three OCP case series, two cicatricial pemphigoid case series, one OCP case report, four MMP case reports, and one cicatricial pemphigoid case report in Latin American population[11-12,20-28]. No prevalence, nor incidence, reports of OCP were found in South America.

It is also relevant to race-association. No race predominance has been reported[4], but some case series and cross-sectional studies have reported a higher prevalence in Caucasian patients[7,29-30]. No ethnic characteristics were registered in the databases used in this study; thus, no results regarding this issue are presented. As it is a controversial topic, it would be important to make emphasis on this issue in future investigations. This may elucidate whether it may be a race-associated trait, as described in previous studies. It is difficult to perform this kind of analysis in Colombia, due to the data scarcity in government bases.

Regarding sex distribution, disease predilection for females has been described in different studies[4-5,29,31]. Nevertheless, male predilection has also been reported[18]. Our results showed a female predilection comparable to the study made in 1981 by Mondino and Brown[31], reporting a male to female ratio of 1:1.6, which is the same we found in our population.

Considering age, different studies reported a mean age of onset between 50 and 70 years old[4-5,29,31]; yet, the age of presentation may vary between 20 and 90y[5,18]. Furthermore, there are some reports in pediatric population[5,30-31]. Differently, our results showed a higher OCP prevalence in older ages, possibly due to a delayed consultation and detection of the disease. This could be attributed to limitations in specialized medical examination access in our country. For this reason, we recommend carrying out further analytical studies on this disease in Colombia and Latin America; it is crucial to identify if the cause is due to our phenotype or if limitations are leading us to a late diagnosis, requiring new public health strategies.

Regarding the demographic distribution of the disease, it might be attributed to a bigger population and a wider availability of specialized centers in the departments with higher prevalence. Our study and other studies have reported a higher prevalence of autoimmune diseases in Antioquia and the Colombian coffee zone. This might be attributed to an European ancestry predominance in these locations[32]. Owing that, it would be crucial to carry out further studies in these areas to identify which factors are involved in the greatest number of autoimmune diseases and thus implement public health politics in this population.

Finally, it is important to consider other aspects such as genetic and socioeconomic factors. Several genetical associations have been described, mostly related to HLA antigens. Some of them are HLA-DQW7, HLA-DQW3, and HLA-DQB1*0301[33-35]. This suggest that there is an immunogenetic susceptibility to develop the disease[36] and may lead to future biomarkers and new mechanisms to optimize the diagnostic approach. Nevertheless, there are no genetic OCP studies in South America, yet. Regarding socioeconomic factors, patients must have a multidisciplinary medical attention and should be educated about the disease, the potential consequences and the therapy. These factors may decrease disease progression and benefit the patient management and adherence to treatment. In Colombia, there are few ocular immunology and uveitis specialists, the initial consultation with these specialists may take a mean of 2.08y[37] which may result in an accelerated progression of the disease and complications, such as blindness.

Limitations SISPRO database limitations should be considered. The most important one is related to a possible under-registration rate due to a lack of OCP awareness, as well as to a limited access to health and technology in remote areas. This may cause delay in the diagnosis. Therefore, it is important to encourage awareness regarding OCP and its notification and registry in this database.

In the same way, the database does not allow knowing the ethnic characteristics of those registered, as well as does not allow staging the severity or the follow up of the disease. Moreover, it is necessary to study with greater detail the distribution of prevalence in the different regions of the country.

Other important issue to consider is that this database reports epidemiologic but not diagnostic approach data. This is the reason why techniques used to reach the final diagnosis are not reported.

Finally, due to the characteristics of the SISPRO[14] dynamic tables, the patients' primary diagnosis may change from one year to another or not be maintained over the years. Therefore, incidence and prevalence may present a slight variation. Nevertheless, the OCP diagnosis code is mostly used by ophthalmologists, which ensures a higher reliability in the diagnosis.

Despite this, nowadays it is the only official database of the government associated with the majority medical care centers in Colombia.

In conclusion, there are important differences between worldwide and Colombian OCP prevalence and incidence data, which may be related to genetic and epigenetic factors, and to the possible underdiagnosis of the disease. Colombian incidence and prevalence are much lower than the ones reported in the literature. The described results about gender ratio are like those mentioned in the medical literature. Nevertheless, our results showed a different age distribution, with higher prevalence of OCP at older age compared to the previous literature reports.

It will be crucial to carry out further analytic studies to identify if this is a specific characteristic of our population or if the delayed diagnosis could be an additional explanation for this specific age distribution.

According to the low prevalence found in SISPRO database from 2009 to 2019, we can consider OCP as a rare and orphan disease in Colombia. Nevertheless, it is important to encourage awareness of the disease due to its devastating consequences.

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REFERENCES

1 Higgins GT, Allan RB, Hall R, Field EA, Kaye SB. Development of ocular disease in patients with mucous membrane pemphigoid involving the oral mucosa. *Br J Ophthalmol* 2006;90(8):964-967.

2 Fremont F, Pelissier-Suarez C, Fournié P, Porterie M, Thevenin A, Astudillo L, Paricaud K, Gualino V, Soler V, Pugnet G. Clinical characteristics and outcomes of ocular cicatricial pemphigoid: a cohort study and literature review. *Cornea* 2019;38(11):1406-1411.

3 Ahmed M, Zein G, Khawaja F, Foster CS. Ocular cicatricial pemphigoid: pathogenesis, diagnosis and treatment. *Prog Retin Eye Res* 2004;23(6):579-592.

4 Foster CS. Cicatricial pemphigoid. *Trans Am Ophthalmol Soc* 1986;84:527.

5 Williams GP, Radford C, Nightingale P, Dart JK, Rauz S. Evaluation of early and late presentation of patients with ocular mucous membrane pemphigoid to two major tertiary referral hospitals in the United Kingdom. *Eye* (*Lond*) 2011;25(9):1207-1218.

6 Saw VP, Dart JK, Rauz S, Ramsay A, Bunce C, Xing W, Maddison PG, Phillips M. Immunosuppressive therapy for ocular mucous membrane pemphigoid strategies and outcomes. *Ophthalmology* 2008;115(2): 253-261.e1.

7 Miserocchi E, Baltatzis S, Roque MR, Ahmed AR, Foster CS. The effect of treatment and its related side effects in patients with severe ocular cicatricial pemphigoid. *Ophthalmology* 2002;109(1):111-118.

8 Letko E, Miserocchi E, Daoud YJ, Christen W, Foster CS, Ahmed AR. A nonrandomized comparison of the clinical outcome of ocular involvement in patients with mucous membrane (cicatricial) pemphigoid between conventional immunosuppressive and intravenous immunoglobulin therapies. *Clin Immunol* 2004;111(3): 303-310.

9 Duke-Elder S. Conjunctiva. *En: System of Ophtalmology* 1965;506.

10 Smith RC, Myers EA, Lamb HD. Ocular and oral pemphigus: report of a case with anatomic findings in the eyeball. *Arch Ophthalmol* 1934;11(4):635-640.

11 Chiganer EH, Albera P. Penfigoide ocular cicatricial: hallazgos de Biopsia conjuntival y su relación con la inflamación y cicatrización ocular. *Revista Mexicana De Oftalmol* 2017;91(3):134-141.

12 Palau AE-B, González-González LA, Rodríguez-García A. Presentación clínica y manejo del penfigoide cicatrizal ocular en México. *Rev Mex Oftalmol* 2010;84(1):10-18.

13 Departamento Administrativo Nacional de Estadística (DANE). [citado 26 de octubre de 2020]. https://www.dane.gov.co/index.php/en/

14 SISPRO - Sistema Integrado de Información de la Protección Social. [citado 26 de octubre de 2020]. https://www.sispro.gov.co/Pages/Home.aspx

15 Lever WF. Pemphigus. *Arch Derm Syphilol* 1942;46(6):800.

16 Bedell AJ. Ocular pemphigus: a clinical presentation of kodachromes. *Trans Am Ophthalmol Soc* 1964;62:109-122.

17 Bettelheim H, Kraft D, Zehetbauer G. On the so-called ocular pemphigus (pemphigus ocularis, pemphigus conjunctivae). *Klinische Monatsblatter Fur Augenheilkunde* 1972;160(1):65-75.

18 Radford CF, Rauz S, Williams GP, Saw VP, Dart JK. Incidence, presenting features, and diagnosis of cicatrising conjunctivitis in the United Kingdom. *Eye* (*Lond*) 2012;26(9):1199-1208.

19 de Carvalho CHP, Santos BRMD, de Castro Vieira C, de Araújo Lima EDN, de Andrade Santos PP, de Almeida Freitas R. Estudo epidemiológico das doenças dermatológicas imunologicamente mediadas na cavidade oral. *An Bras Dermatol* 2011;86(5):905-909.

20 Jalil BA, Abdou YG, Rosen SA, Dammad T. Mucous membrane pemphigoid causing central airway obstruction. *J Bronchol Interv Pulmonol* 2017;24(4):334-338.

21 Miziara ID, Sperandio F, Bohadana SC, Braga N, Romano FR, Miniti A. Cicatricial pemphigoid: report of five cases. *Ear Nose Throat J* 2002;81(7):442-448.

22 Louie TD. Ocular cicatricial pemphigoid: case report. *J Am Optom Assoc* 1998;69(3):153-160.

23 Lourenço SV, Boggio P, Agner Machado Martins LE, Santi CG, Aoki V, Menta Simonsen Nico M. Childhood oral mucous membrane pemphigoid presenting as desquamative gingivitis in a 4-year-old girl. *Acta Derm Venereol* 2006;86(4):351-354.

24 Méndez-Bermúdez IJ, Maldonado-Cerda A, Marrero-Barrera F, Oliver-Cruz AL. Characteristics upon presentation of ocular mucous membrane pemphigoid patients in Puerto Rico. *Puerto Rico Heal Sci J* 2020;39(1):34-38.

25 Malbrán A, Juri MC, Brunzini R, Devoto M, Georgiett D, Larrauri B, Torre MG, Malbrán E. Recalcitrant cicatrizing conjunctivitis. Treatment of nine patients with rituximab. *Medicina (B Aires)*. 2019;79(4):299-302.

26 Barbosa LDN, Silva RSD, Verardino GC, Gripp AC, de Fátima Guimarães Scotelaro Alves M. Penfigoide de membranas mucosas com estenose esofágica grave. *An Bras Dermatol* 2011;86(3):565-568.

27 Oliveira PC, Reis Junior JA, Lacerda JA, Silveira NT, Santos JM, Vitale MC, Pinheiro AL. Laser light may improve the symptoms of oral lesions of cicatricial pemphigoid: a case report. *Photomed Laser Surg* 2009;27(5):825-828.

28 Orrico SR, Navarro CM, Rosa FP, Reis FA, Salgado DS, Onofre MA. Periodontal treatment of benign mucous membrane pemphigoid. *Dent Today* 2010;29(7):100-102; quiz 102-103.

29 Ong HS, Setterfield JF, Minassian DC, *et al*. Mucous membrane pemphigoid with ocular involvement. *Ophthalmology* 2018;125(4): 496-504.

30 Rauz S, Maddison PG, Dart JK. Evaluation of mucous membrane pemphigoid with ocular involvement in young patients. *Ophthalmology* 2005;112(7):1268-1274.

31 Mondino BJ, Brown SI. Ocular cicatricial pemphigoid. *Ophthalmology* 1981;88(2):95-100.

32 Londoño J, Peláez Ballestas I, Cuervo F, *et al*. Prevalencia de la enfermedad reumática en Colombia, según estrategia COPCORD-Asociación Colombiana de Reumatología. Estudio de prevalencia de enfermedad reumática en población colombiana mayor de 18 años. *Revista Colombiana De Reumatología* 2018;25(4):245-256.

33 Ahmed A R, Foster S, Zaltas M, Notani G, Awdeh Z, Alper C A, Yunis E J. Association of DQw7 (DQB1*0301) with ocular cicatricial pemphigoid. *Proc Natl Acad Sci U S A* 1991;88(24):11579-11582.

34 Yunis JJ, Mobini N, Yunis EJ, Alper CA, Deulofeut R, Rodriguez A, Foster CS, Marcus-Bagley D, Good RA, Ahmed AR. Common major histocompatibility complex class II markers in clinical variants of cicatricial pemphigoid. *Proc Natl Acad Sci U S A* 1994;91(16):7747-7751.

35 Zakka LR, Reche P, Ahmed AR. Role of MHC Class II genes in the pathogenesis of pemphigoid. *Autoimmun Rev* 2011;11(1):40-47.

36 Mondino BJ, Brown SI, Rabin BS. HLA antigens in ocular cicatricial pemphigoid. *Arch Ophthalmol* 1979;97(3):479.

37 Villalobos-Pérez A, Reyes-Guanes J, Muñoz-Ortiz J, Estévez-Florez MA, Ramos-Santodomingo M, Balaguera-Orjuela V, De-La-torre A. Referral process in patients with uveitis: a challenge in the health system. *Clin Ophthalmol* 2021;15:1-10.