Received: 28 Sep 2022 | **Accepted:** 23 Jan 2023 **Genel Tıp Derg. Volume** 33/**Issue** 1 (February), 25-29
DOI: 10.54005/geneltip.1150171

ORIGINAL ARTICLE

The Evaluation Retinal Toxicity of Intravitreal Infliximab Injection

Intravitreal İnfliximab İnjeksiyonun Retinal Toksitesinin Değerlendirilmesi

[1]Muhamet Kıvılcım

[1]Private Akdeniz Hospital, Antalya

Correspondence

Muhamet Kıvılcım, Özel Akdeniz Hastanesi Manavgat Antalya

E-Mail: muhamet_kivilcim@yahoo.com

How to cite ?

Kıvılcım M. The Evaluation Retinal Toxicity of Intravitreal Infliximab Injection. Genel Tıp Dergisi. 2023; 33(1): 25-29.

ABSTRACT

Objective: The aim of this study was to evaluate the toxicity of different doses of intravitreal injection of inflixamab in rabbits.
Materials and Methods: Twenty New Zeland albino rabbits were used for this study and divided into five groups (n=4 each). The rabbits were injected intravitreally with, 0.125mg 0.250mg, 0.500mg, 1.25mg or 2.5mg Infliximab in 0.1 ml in one eye and 0.1 ml saline solution was used in the contralateral eye. All the animals were examined using indirect ophthalmoscopy and slit-lamp biomicroscopic examination before intravitreal injection and on days 1,7 and 14. ERG was performed before the experiment and on the 14th day after the experiment. On day 14 the animals were euthanized. Histological preparations of the enucleated eyes were examined for retinal toxicity.
Results: In our study we found no retinal toxicity up to 1.25mg groups according to ERG results and Histological signs. In our study, we did not find any ERG or histological toxicity in the group up to 1.25 mg. We concluded a significant decrease in ERG and histological toxicity signs in 1 of 4 eyes of the 2.5 mg group.
Conclusion: Infliximab injection up to 1.25 mg is nontoxic to the rabbit's retina. Intravitreal injection of infliximab may be a useful treatment for Uveitis especially Behcet's disease, diabetic retinopathy, age related macular degeneration and proliferative vitreoretinopathy.

Key words: infliximab, retinal toxicity, intravitreal injection, uveitis, behcet's, diabetic retinopathy

ÖZ

Amaç: Bu çalışmada tavşanlarda farklı dozlardaki intravitreal inflixamab injeksiyonun toksitesinin değerlendirilmesi amaçlanmıştır.
Materyal ve Metod: Çalışmada kullanılan 20 beyaz Yeni Zelanda tavşanı 5 gruba (n=4) ayrılmıştır. Tavşanların bir gözüne intravitreal olarak 0,125 mg, 0,250 mg, 0,500 mg, 1,25 mg ve 2,5 mg inflixmab 0,1 tuzlu solüsyon içinde enjekte edilmiştir. Kontrol gözüne 0,1 tuzlu solüsyon olarak uygulanmıştır. Tüm hayvanların deneyden önce ve deneyden sonraki 1., 7., ve 14. günde indirek oftalmoskopi ve yarık lamba biyomikroskopi muayeneleri yapılmıştır. ERG deneyden önce ve deney sonrası 14. günde yapılmıştır. Hayvanlara 14. günde ötonazi uygulanmıştır. Enükleasyon edilen gözlerin histolojik örnekleri retina toksidi açısından incelenmiştir.
Bulgular: Çalışmamızda 1,25 mg doza kadar olan grupta ERG ve histolojik olarak bir toksite bulmadık. 2,5 mg grubun 4 gözünden birinde ERG'sinde anlamlı azalma ve histoojik toksite bulguları saptadık.
Sonuç:1,5 mg doza kadar olan inflixmab injeksiyonu tavşan retinasında non toksiktir. İntravitreal inflixmab injeksiyonu üveitlerde özellikle behçet hastalığında diyabetik retinopatide, yaşa bağlı makula dejenerasyonunda ve proliratif vitreo retinopatide yararlı bir tedavi olabilir.

Anahtar Kelimeler: infliximab, retinal toksite, üveit, behçet hastalığı, diyabetik retinopati

Introduction

Diabetic retinopathy and Uveitis are major causes of vision loss and other ocular complications (1,2). Corticosteroids and immunosuppressive treatment is the primary therapy for uveitis (3). Laser photocoagulation treatment is the main therapy for diabetic retinopathy (2,4). However, all these treatments have serious side effects and sometimes are not effective (5-7). Current research focuses on the most beneficial treatments with fewer side effects for uveitis and diabetic retinopathy. Intra vitreal infliximab maybe good adjuvant treatment for these diseases.

Infliximab is monoclonal antibody with a molecular weight of 149K Daltons. It contains both human constant and murine variable regions. It is made up of human and mouse antibodies. Infliximab is an artificial antibody which is originally developed from mouse. Due to human immune reaction against mouse proteins, mouse common domains are replaced by human antibody domains.

TNF-alpha is a pro-inflammatory cytokine shown in high levels in the vitreous in proliferative vitreoretinopathy and proliferative diabetic retinopathy (8). Diabetic retinopathy has been associated TNF-alpha gene polymorphism and expression of HLA-DR3 and HLA-DR4 phenotypes (9). Petros Sficakis et al. published intravenous infliximab using after two sessions argon laser treatment in refractory diabetic macular edema cases increased visual acuity more than placebo laser groups (10). Therefore, anti-TNF-alpha drugs may be adjunct therapy for the diabetic retinopathy and proliferative vitreoretinopathy (PVR).

Clinically many cases have shown that infliximab has been beneficial in treating uveitis especially Behcet's disease (9-12). Also many experimental studies have reported that anti TNF-alpha treatment prevents endotoxin induced uveitis (EIU) in animal models (13).

Some experimental studies of intravitreal infliximab have

Peer-Review: Double anonymized - Two External
Plagiarism Checks: Yes - Turnitin
Complaints: geneltip@selcuk.edu.tr

been shown to reduce the development of PVR (14) and inhibition of choroidal neovascularization (15).

Also, it was determined the combination of intravitreal Avastin and infliximab prevented the leakage of choroidal effusion and decreased macular thickness in age-related macular degeneration (ARMD) patients (16).

Recently, intravitreal injection is commonly used in ophthalmology for retinal and choroidal diseases. There are many advantages of intravitreal injection. However, retinal toxicity is a primary concern when using intravitreal injection. Our purpose is to determine what intravitreal doses of infliximab are nontoxic for the retina.

Material and Methods

Animals

Twenty New Zealand albino rabbits weighing between 2-3 kg were used for this study. Rabbits were treated in accordance with principles of the Association for Research in Vision and Ophthalmology (ARVO) for humane treatment of animals. Principles of laboratory animal care (NIH publication No. 85-23, revised 1985), the OPRR Public Health Service Policy on the Humane Care and Use of Laboratory Animals (revised 1986), and the U.S. Animal Welfare Act were followed. The study was conducted in the research laboratory of Tulane University, Faculty of Medicine. Only one eye was used for experimental purposes, with the fellow eye serving as a control. Slit lamp and indirect fundoscopic examination was performed on all eyes prior to the study and on days 1,7, and 14 after intravitreal injection. Any animals demonstrating corneal, lens opacity or retinal damage prior to the study were excluded. Similarly, the animals were examined after intravitreal injection and before they were euthanized. The animals were anesthetized prior to all procedures using approximately 1 ml of a mixture of ketamine hydrochloride (50mg/kg, Ketalar; Yuhan Co., Seoul, South Korea) and xylazine hydrochloride (5mg/kg,Indian immunological Ltd., India). The eyes were dilated by topical application of phenylephrine (2.5%) and tropicamide (0.5%). Topical anesthesia was applied using proparacaine (0.5%). The animals were sacrificed 2 weeks after intravitreal injection by an intravenous injection of 100mg/kg sodium pentobarbital.

Intravitreal Injections

All procedures were performed under sterile conditions using an operating microscope for visualization. Both eyes were used on each animal with one eye receiving the treatment and the other receiving sterile BSS, serving as a control. Anterior chamber tap was performed with a 25 G needle withdrawing 0.1 cc of aqueous fluid to reduce intraocular pressure and to minimize drug reflux following injection. Intravitreal injection was performed using a 30 G needle attached to a tuberculin syringe inserted bevel up approximately 2 mm posterior to limbus. Five different doses of infliximab (Remicade;Centocor Ortho Biotech Inc, Horsham, PA) were prepared in 0.1 ml: 0.125mg, 0.250mg, 0.500mg, 1.25mg and 2.5 mg. Each concentration was injected in one eye of the four rabbits, and 0.1 ml volume of sterile BSS was injected into the contralateral eye. A slit lamp and fundoscopic examination was performed and the animals were observed for two weeks for signs of infection, inflammation and toxicity.

Electrophysiological Tests

Electroretinogram (ERG) using the UTAS-2000 system (LKC technology) was performed prior to intravitreal injection and 14 days after injection. The rabbits were adapted to the dark for at least 30 minutes after pupillary dilation. Unipolar contact lenses (ERG jet electrodes) were put on both corneas with goniosol (IOLab Corporation); the negative electrode was placed in the subcutaneous space of the forehead, and the ground electrode was clipped to the earlobe with some electric gel. The dark-adapted scotopic response (step 1, Rod response), scotopic flash response (step 2, Maximal response, cone+ rod) and (after waiting for 3 minutes) light adapted photopic response (step 4, Cone response) was recorded. The average of 5 sweeps was determined for each step. The difference of a and b waves was calculated for each step. The baseline was compared to the response two weeks after injection. A decrease in the post injection response over 30 % was considered significant.

Histological Examination

Following the final ERG session, all the rabbits were euthanized with intravenous injection of sodium pentobarbital. The eyes were enucleated and fixed in karnovsky fixative for 48 hours and then processed, sectioned, and stained with hematoxylin and eosin for light microscopy.

Results

Clinical Examination

Fundus examination was performed on all the eyes immediately after intravitreal injection and prior to euthanasia. No corneal opacity, cataract, vitreous hemorrhage, retinal detachment or optic atrophy was seen in any of the eyes.

Electrophysiological Tests

ERG changes were considered significant if the follow-up differences in (a and b) amplitude were decreased more than 30 %. The follow up ERGs in 1out of the 4 eyes in the 2.5 mg infliximab group showed approximately 30% decrease in scotopic response (step1 and step2) but photopic response(step4) did not show significant decrease. (Fig.1) The other eyes showed no significant decreases (Table 1).

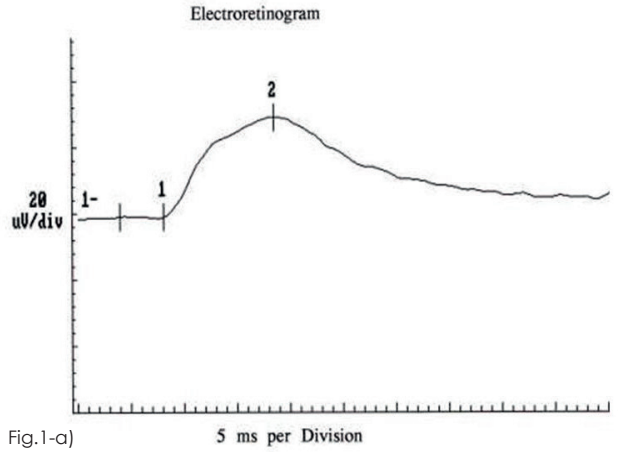

Fig.1-a)

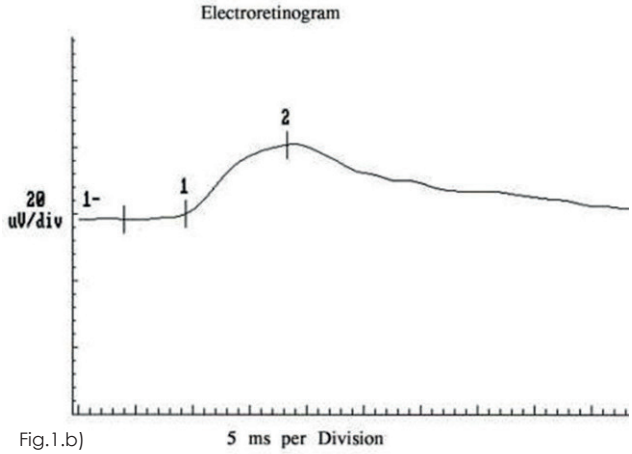

Fig.1.b)

Fig1: Baseline Step 1 ERG(a), Endpoint (14 days after injection) Step1 ERG in the highest dose group. b) There is a significant decrease (approximately 25%) between baseline and endpoint ERG.

Table 1. The evaluation retinal toxicity of intravitreal infliximab injection.

Group	ERG Step 1 Rod Response	ERG Step 2 Cone + Rod Response	ERG Step 3 Cone Response
Control	No significant decrease	No significant decrease	No significant decrease
0.125 mg	No significant decrease	No significant decrease	No significant decrease
0.250 mg	No significant decrease	No significant decrease	No significant decrease
0.500 mg	No significant decrease	No significant decrease	No significant decrease
1.25 mg	No significant decrease	No significant decrease	No significant decrease
2.5 mg	Decrease in one eye (minimal retinal toxicity in same eye histology)	Decrease in one eye (same eye showed decrease in Step 1 ERG)	No significant decrease

Histological Examination

Light microscopy was performed on all eyes. Toxic findings were not seen in up to 1.25 mg groups of infliximab.

However, 1 of the 4 eyes at 2.5 mg group showed minimal toxicity. The minimal toxicity that was found in this eye was due to many inflammatory cells in the ora serrata and around apex of the ciliary body. (Fig.2) The rest of the retina in this eye was not damaged. This eye also showed significant decrease in scotopic response.

In this article, statistical analysis is not mentioned because of its content and methodology.

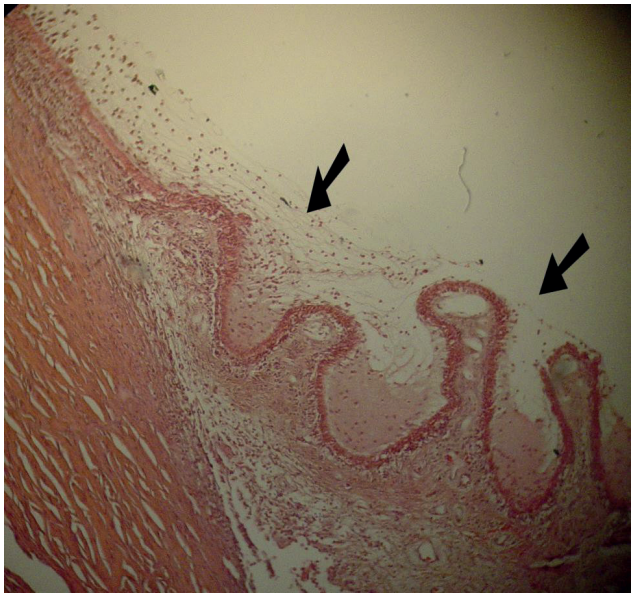

Fig 2: Many inflammatory cells are in the ora serrata and around apex of corpus ciliare in the highest dose group.

Discussion

Intercellular adhesion molecule-1 (ICAM-1) and Leukocyte integrin CD18 are very important molecules in animals with diabetic retinopathy (18-20) and uveitis model (21-23). Antibody against ICAM-1 and CD18 in the rat model prevents diabetic retinopathy by reducing leukocyte adhesion which induce a breakdown in the blood retinal barrier resulting in the endothelial injury (19,20). Clinical trials performed with or without laser photocoagulation treatment showed that aspirin (650 mg daily) had no effect on diabetic retinopathy (24).

Intravitreal use of infliximab may be the main or adjuvant therapy in diabetic macular edema. Clinically many reports have stated that infliximab has some beneficial effects in uveitis (7,11-14) Few publications has been made on the use of intravitreal infliximab especially in uveitis (26), diabetic macular edema (26) and ARMD (17).

We found that 1.25mg/ml of intravitreal infliximab had no retinal toxicity and one eye in 2.5mg/ml group had histological toxicity and significant decrease in ERG

in rabbit eyes. Another study showed that 2 mg of infliximab had no retinal toxicity while 3.3mg infliximab had retinal toxicity in rabbit eyes (27). It was reported that two and three monthly intravitreous injections of 2 mg infliximab to rabbits showed no change in histological and electroretinographic tests and clinical evaluations (28).

Another study concluded that intravitreal infliximab at doses up to 1.25 mg was not toxic to the retina (29).

While intravitreal injection of a dose of 1.5 mg/0.1 ml of infliximab has no toxic effect on retinal integrity in rabbits, it has been stated that a higher dose of 7.5 mg/0.1 ml might be slightly toxic (30).

In different studies no statistically significant retinal abnormalities were observed as a result of serial intravitreal injections of 2.0 mg infliximab (31) and little or no damage was found in the eyes of rabbits injected with infliximab (32). Also it was reported that intravitreal infliximab could inhibit the growth of CNV in a rat model of age-related macular degeneration (33).

Clinically using 2 mg dose of infliximab intravitreally had some uveitic reaction treated by corticosteroid (26,27), on the other hand, 1mg dose of infliximab use did not show any uveitic reactions (26). Similarly, in our study one eye of 2.5 mg group had significant inflammatory reaction on ora serrata area. We thought that the cause of inflammation was not infection during intravitreal procedure or needling etc. It was probably related to intravitreal injection, and this focal area could have received highest drug concentration than other place.

Currently intravitreal injections of corticosteroid and others are successfully used for treatment of uveitis (27), and diabetic retinopathy (34). The use of steroids for retinal diseases is gaining widespread acceptance(35). Moreover, the effectiveness of steroids againist complications of retinal diseases such as vitritis(3) or macular edema(36) has been well documented. A recent study proved that intravitreal injection of steroids or steroid implants might be useful in controlling postoperative inflammation for uveitis cataract (37). It was reported that intraoperative intravitreal injection of triamcinolone might be safe and beneficial for patients with chronic idiopathic anterior uveitis or intermediate uveitis (38). In another study, successful results were obtained with intravitreal injections for diabetic retinopathy, age-related macular degeneration, and retinal vein occlusion (39).

Anti TNF-alpha drugs have few but serious side effects when used systemically such as heart failure, lymphoma. Intravitreal injection of up to 1.25 mg of infliximab may be a beneficial way to treat uveitis, PVR, ARMD and diabetic retinopathy without inducing serious systemic side effects.

The rabbit model is widely used to find non-toxic doses of intravitreal drugs in the human eye. There are similarities and differences between the human eye and the rabbit eye. For example, the average rabbit vitreous volume is 1.5 ml, but it is 4.5 ml in the human eye (40), which may cause differences in drug concentration in the vitreous. These differences should be taken into consideration when evaluating the results.

Conclusion

Up to 1.25 mg of intravitreal injected Infliximab appears to be nontoxic to the retina in the rabbit eyes. It can be an adjunct drug for treatment of uveitis, ARMD, PVR and diabetic retinopathy.

Acknowledgements

We would like to thank emeritus Prof.Dr Gholam A. Peyman for providing us the opportunity to work in his research laboratory under his supervision.

References

1.Suttorp-Schulten MS, Rothova A. The possible impact of uveitis in blindness: a literature survey. Br. J. Ophthalmology 1996; 80: 844-8

2.Gurelik G, Coney JM, Zakov ZN. Binocular indirect panretinal laser photocoagulation for the treatment of proliferative diabetic retinopathy. Ophthalmology Surgery Lasers&Imaging 2004; 35: 94-102

3.Kramer M, Ehrlich R., Snir M, Friling R, Mukamel M, Weinberger D, et al. Intravitreal injections of triamcinolone acetonide for severe vitritis in patients with incomplete Behcet's disease. American Journal of Ophthalmology 2004; 138(4): 666-667

4.Stitt AW, Curtis TM, Chen M, Medina RJ, McKay GJ, Jenkins A, et al. The progress in understanding and treatment of diabetic retinopathy. Progress in Retinal and Eye Research 2016; 51: 156-186.

5.Jabs DA, Rosenbaum JT, Foster CS, Holland GN, Jaffe GJ, Louie JS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am. J Ophthalmology 2000; 130: 492-513

6.Meredith TA., Kertes PJ, Conway MD. The diabetic retinopathy vitrectomy study. Clinical Trials in Ophthalmology 1998; 37-48

7.Murphy CC, Ayliffe WH, Booth A, Makanjuola D, Andrews PA, Jayne D. Tumor necrosis factor alpha blockade with infliximab for refractory uveitis and scleritis. Ophthalmology 2004; 111: 352-6

8.Limb GA, Hollifield RD, Webster L, Charteris DG, Chignell AH. Soluble TNF receptors in vitreoretinal proliferative disease. Invest Ophthalmology Vis Sci 2001; 42: 1586-91

9.Hawrami K, Hitman GA, Rema M, Snehalatha C, Viswanathan M, Ramachandran A, et al. An association in non-insulin-dependent diabetes mellitus subjects between susceptibility to retinopathy and tumor necrosis factor polymorphism. Huma Immunology 1996; 46(1): 49-54

10.Sfikakis, PP, Grigoropoulos V, Emfietzoglou I, Theodossiadis G, Tentolouris N, Delicha, E, et al. Infliximab for diabetic macular edema refractory to laser photocoagulation: a randomized, double-blind, placebo-controlled, crossover, 32-week study. Diabetes Care 2010; 33(7): 1523-1528

11.Ohno S, Nakamura S, Hori S, Shimakawa M, Kawashima H, Mochizuki M, et al. Efficacy, safety, and pharmacokinetics of multiple administration of Infliximab in Behcet's disease with refractory uveoretinitis. J. Rheumatol 2004; 31: 1362-8

12.Falappone PCF, Iannone F, Scioscia C, Grattagliano V, Covelli M, Lapadula, G. The treatment of recurrent uveitis with TNFa inhibitors. Reumatismo 2004; 56(3): 185-189

13.Calvo-Río V, Blanco R, Beltrán E, Sánchez-Bursón J, Mesquida M, Adán A, et al. Anti-TNF-a therapy in patients with refractory uveitis due to Behçet's disease: a 1-year follow-up study of 124 patients. Rheumatology 2014; 53(12): 2223-2231

14.Lejoyeux R, Diwo E, Vallet H, Saadoun D, Tezenas du Montce, S, Bodaghi B, et al. Infliximab and adalimumab in uveitic macular edema. Ocular Immunology and Inflammation 2018; 26(7): 991-996

15.Sartani G, Silver PB, Rizzo LV, Chan CC, Wiggert B, Mastorakos G, et al. Anti-tumor necrosis factor alpha therapy suppresses the induction of experimental autoimmune uveoretinitis in mice by inhibiting antigen priming. Invest. Ophthalmol. Vis. Sci 1996; 37: 2211-8

16.Savur F, Aydemir O, İlhan N. The effect of infliximab and octreotide on cytokine levels experimental proliferative vitreoretinopathy. Cutaneous and Ocular Toxicology 2020; 39(1): 61-66

17.Freitas LGAD, Isaac DLC, Tannure WT, Gabriel LAR, Reis RGD, Rassi AR, et al. Intravitreal bevacizumab combined with infliximab in the treatment of choroidal neovascularization secondary to age-related macular degeneration: case report series. Arquivos Brasileiros de Oftalmologia 2013; 76: 180-184

18.Barouch FC, Miyamoto K, Allport JR, Fujita K, Bursell SE, Aiello LP, et al. Integrin-mediated neutrophil adhesion and retinal leukostasis in diabetes. Investigative Ophthalmology & Visual Science 2000; 41(5): 1153-1158

19.Miyamoto MK, Khosrof S, Bursell SE, Rohan R, Murata T, Clermont AC, et al. Prevention of leukostasis and vascular leakage in streptozotocin-induced diabetic retinopathy via intercellular adhesion molecule-1 inhibition. Proceedings of the National Academy of Sciences 1999; 96(19): 10836-10841

20.Joussen AM, Murata T, Tsujikawa A, Kirchhof B, et al. (2001). Leukocyte-mediated endothelial cell injury and death in the diabetic retina. The American Journal of Pathology 158(1): 147-152

21.Kanagawa T, Matsuda S, Mikawa Y, Kogiso M, Nagasawa H, Himeno K, et al. Role of ICAM-1 and LFA-1 in endotoxin-induced uveitis in mice. Japanese journal of ophthalmology 1996; 40(2): 174-180

22.Whitcup SM, Hikita N, Shirao M, Miyasaka M, Tamatani T, Mochizuk M, et al. Monoclonal antibodies against CD54 (ICAM-1) and CD11a (LFA-1) prevent and inhibit endotoxin-induced uveitis. Experimental Eye Research 1995; 60(6): 597-601

23.Rosenbaum JT, Boney RS. Efficacy of antibodies to adhesion molecules, CDlla or CD18, in rabbit models of uveitis. Current Eye Research 1993; 12(9): 827-831

24.ETDRS Research Group. Effects of aspirin treatment on diabetic retinopathy. ETDRS report number 8. Ophthalmology 1991; 98(5): 757-765

25.Hamza, MM, Macky TA, Sidky MK, Ragab G, Soliman MM. Intravitreal infliximab in refractory uveitis in Behçet's disease: a safety and efficacy clinical study. Retina 2016; 36(12): 2399-2408

26.Wu L, Hernandez-Bogantes E, Roca JA, Arevalo JF, Barraza K, Lasave AF. Intravitreal tumor necrosis factor inhibitors in the treatment of refractory diabetic macular edema: a pilot study from the Pan-American Collaborative Retina Study Group. Retina 2011; 31(2): 298-303

27.Giansanti F, Ramazzotti M, Vannozzi L, Rapizzi E, Fiore T, Iaccheri B, et al. A pilot study on ocular safety of intravitreal infliximab in a rabbit model. Investigative Ophthalmology & Visual Science 2008; 49(3): 1151-1156

28.Rassi AR, Rigueiro MP, Isaac DLC, Dourado L, Abud MB, Freitas ÉC, et al. A safety study of retinal toxicity after serial intravitreal injections of infliximab in rabbits eyes. Arquivos Brasileiros de Oftalmologia 2011; 74: 352-356

29.Kazi AA, Kivilcim M, Peyman GA, Khan P, Trost L. Intravitreal toxicity of infliximab. Investigative Ophthalmology & Visual Science 2006; 47(13): 4298-4298

30.Zayit-Soudry S, Vainer I, Zemel E, Mimouni M, Rabena M, Pieramici DJ, et al. Infliximab exerts a dose-dependent effect on retinal safety in the albino rabbit. Documenta Ophthalmologica 2017; 135(3): 175-185

31.Alves LD, Rassi AR, Rigueiro M, Abud MB, Freitas EC, Carneiro LB, et al. A safety study of serial intravitreal injections of Infliximab in the rabbit. Investigative Ophthalmology & Visual Science 2011; 52(14): 5650-5650

32.Rabena M, Pieramici D, Soudry S, Zemel E, Loewenstein A, Perlman I, et al. Safety of Intravitreal Infliximab in a Rabbit Model. Investigative Ophthalmology & Visual Science 2009; 50(13): 3859-3859

33.Olson JL, Courtney RJ, Mandava N. Intravitreal infliximab and choroidal neovascularization in an animal model. Archives of Ophthalmology 2007; 125(9): 1221-1224

34.Benítez del Castillo Sánchez JM, García Sánchez J. Inyección intravítrea de triamcinolona acetónido en uveitis no infecciosas. Arch. Soc. Esp. Oftalmol 2001; 76(11): 661-664

35.Ciulla TA, Walker JD, Fong DS, Criswell MH. Corticosteroids in posterior segment disease: an update on new delivery systems and new indications. Current Opinion in Ophthalmology 2004; 15(3): 211-220

36.Jonas JB, Hayler JK, Söfker A, Panda-Jonas S. Intravitreal injection of crystalline cortisone as adjunctive treatment of proliferative diabetic retinopathy. American Journal of Ophthalmology 2001; 131(4): 468-471

37.Hsieh YH, Jhou HJ, Chen PH, Hwang YS. Intravitreal injection versus systematic treatment in patients with uveitis undergoing cataract surgery: a systematic review and meta-analysis. Graefe's Archive for Clinical and Experimental Ophthalmology 2022; 1-12

38.Dada T; Dhawan M, Garg S, Nair S, Mandal S. Safety and efficacy of intraoperative intravitreal injection of triamcinolone acetonide injection after phacoemulsification in cases of uveitic cataract. Journal of Cataract & Refractive Surgery 2007; 33(9): 1613-1618

39.Saleh OA, Jammal H, Alqudah N, Alqudah A, Abu-Yaghi N. Clinical Experience in the Administration of Intravitreal Injection Therapy at a Tertiary University Hospital in Jordan During the COVID-19 Lockdown. Clinical Ophthalmology 2020 Aug 24; 14: 2473-2480

40.Antcliff RJ, Spalton DJ, Stanford MR, Graham EM, Marshall J. Intravitreal triamcinolone for uveitic cystoid macular edema: an optical coherence tomography study. Ophthalmology 2001; 108(4): 765-772