

# **THE RECENT TRENDS IN MANAGEMENT OF REFRACTORY UVEITIS**

*Essay submitted for partial fulfillment of the Master Degree in Ophthalmology*

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# الطرق الحديثة لعلاج الإلتهاب المستعصي للجهاز العنبي

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# **Contents**

<b>Subject</b>	<b>Page</b>
Acknowledgements.....	<b>i</b>
Contents.....	<b>ii</b>
List of abbreviations.....	<b>iii</b>
List of Figures.....	<b>v</b>
List of Tables.....	<b>viii</b>
List of Boxes.....	<b>ix</b>
Introduction.....	<b>1</b>
Aim of the Work .....	<b>3</b>
Anatomy of The Uveal Tract.....	<b>4</b>
Epidemiology of Uveitis.....	<b>8</b>
Pathology of Refractory Uveitis.....	<b>13</b>
Diagnosis of Refractory Uveitis.....	<b>18</b>
Treatment of Refractory Uveitis.....	<b>52</b>
Work Up for Specific Disease Entities.....	<b>97</b>
Summary .....	<b>119</b>
References .....	<b>122</b>
Arabic Summary.....	<b>140</b>

## **List of Abbreviation**

<b>ACE</b>	Angiotensin-Converting Enzyme
<b>AIDS</b>	Acquired Immune Deficiency Syndrome.
<b>AMPPP E</b>	Acute Multifocal Posterior Placoid Pigment Epitheliopathy.
<b>ANA</b>	Antinuclear Antibody
<b>ANCA</b>	Antineutrophil Cytoplasmic Antibody.
<b>APC</b>	antigen-presenting cells
<b>ASOT</b>	Antistreptolysin-O Titre.
<b>BD</b>	Behçet Disease.
<b>CD</b>	Cluster of Differentiation
<b>CMV</b>	Cytomegalovirus.
<b>CNV</b>	Choroidal Neovascularization.
<b>DC</b>	dendritic cells
<b>DME</b>	Diabetic Mcular Edema.
<b>DSF</b>	Diffuse Subretinal Fibrosis
<b>FFA</b>	Fundus Fluorescein Angiography.
<b>Fig</b>	Figure.
<b>ECCE</b>	Extracapsular Cataract Extraction .
<b>ESR</b>	Erythrocyte Sedimentation Rate.
<b>HTLV- 1</b>	The Human T-lymphotropic virus Type I
<b>IBD</b>	Inflammatory Bowel Disease.
<b>ICG-A</b>	Indocyanine Green Angiography.
<b>IE</b>	Infective Endocarditis.
<b>IFN-a</b>	Interferon Alpha.
<b>Ig</b>	Immunoglobulin.
<b>IL</b>	Interleukin
<b>IMT</b>	Immunomodulatory Therapy.
<b>IOL</b>	Intraocular Lens.
<b>IOP</b>	Intraocular Pressure
<b>IVTA</b>	Intravitreal Triamcinolone Acetonide.
<b>IU</b>	Intermediate Uveitis.
<b>JRA</b>	Juvenile Rheumatoid Arthritis.

<b>JIA</b>	Juvenile Idiopathic Arthritis.
<b>KPs</b>	Keratic Precipitates.
<b>MCP</b>	Multifocal Choroiditis with Panuveitis
<b>MHC</b>	Major histocompatibility complex
<b>NSAID</b>	Nonsteroidal Anti-Inflammatory Drugs.
<b>OCT</b>	Optical Coherence Tomography.
<b>PCR</b>	Polymerase Chain Reaction.
<b>PIC</b>	Punctate Inner Choroidopathy
<b>PLP</b>	Peripheral Laser Photocoagulation.
<b>POHS</b>	Presumed Ocular Histoplasmosis Syndrome.
<b>PPV</b>	Pars Plana Vitrectomy.
<b>PSCC</b>	Posterior Subcapsular Cataract.
<b>PSII</b>	Posterior segment intraocular inflammation.
<b>PVR</b>	Proliferative Vitreoretinopathy.
<b>RD</b>	Retinal Detachment.
<b>RF</b>	Rheumatoid Factor.
<b>RPE</b>	Retinal Pigmented Epithelium.
<b>SLE</b>	Systemic Lupus Erythematosus.
<b>SO</b>	Sympathetic Ophthalmia.
<b>SPCA</b>	Short Posterior Ciliary Arteries.
<b>STOI</b>	Sight threatening ocular inflammation.
<b>TB</b>	Tuberculosis.
<b>TCR</b>	T-cell receptor
<b>TLR</b>	Toll-like receptor
<b>TINU</b>	Tubulointerstitial nephritis and uveitis
<b>TNF</b>	tumor necrosis factor
<b>VKH</b>	Vogt-Koyanagi-Harada Syndrome
<b>5-FU</b>	5-Fluorouracil

## **List of Figures**

<b>Figure</b>	<b>Page</b>
<b>Fig. 1</b> Activation and polarization of T-cell responses.	<b>14</b>
<b>Fig. 2</b> Activation of an autoinflammatory response.	<b>15</b>
<b>Fig. 3</b> Clinical photographs of acute anterior uveitis	<b>22</b>
<b>Fig 4</b> Binocular indirect ophthalmoscopic grading of vitreal haze	<b>24</b>
	<b>25</b>
<b>Fig 5</b> Snowbanking in pars planitis.	
<b>Fig. 6</b> What can underlie a vitritis?	<b>25</b>
<b>Fig.7</b> Retinal vasculitis.	<b>26</b>
<b>Fig.8</b> Chorioretinitis.	<b>30</b>
<b>Fig. 9</b> Signs in posterior segment intraocular inflammation.	<b>31</b>
<b>Fig. 10</b> various white dot syndromes	<b>32</b>
<b>Fig. 11</b> peripapillary atrophy in a patient with serpiginous choroidopathy.	<b>33</b>
<b>Fig. 12</b> Swollen optic nerve head secondary to sarcoid granuloma.	<b>34</b>
<b>Fig. 13</b> Typical posterior attack in a patient with Behçet's disease	<b>34</b>
<b>Fig. 14</b> Serous retinal detachments in Vogt-	<b>35</b>

Koyanagi-Harada disease.

- Fig. 15** Fundus fluorescein angiography(FFA) in 45 patients with retinal vasculitis.
- Fig. 16** FFA demonstrating active retinal vasculitis, 45 ischemia, and cystoid macular edema in intermediate uveitis.
- Fig. 17** Fundus fluorescein angiography 46 demonstrating extent of multifocal choroidal lesions early in evolution of birdshot choroidopathy.
- Fig. 18** FFA of patients with of intermediate uveitis 46
- Fig. 19** Sight-threatening complication of low-grade 47 noninfectious posterior segment intraocular inflammation.
- Fig. 20** ICG angiography of patient with serpiginous 48 choroidopathy.
- Fig. 21** The benefits of combined FFA and ICGA. 48
- Fig. 22** OCT demonstration of structural changes in 49 refractory uveitis.
- Fig. 23** Documenting resolution of cystoid macular 50 edema.
- Fig. 24** Visual fields to demonstrate loss of visual 51 function.
- Fig. 25** FFA of posterior segment sight-threatening 53 ocular inflammation.
- Fig. 26** Generic algorithm for a suggested scheme 59 for patients with noninfectious PSII.



<b>Fig. 27</b>	Retisert implant	<b>69</b>
<b>Fig. 28</b>	Retisert implant in the eye	<b>69</b>
<b>Fig. 29</b>	<u>Posurdex</u> (Allergan.Inc.)	<b>69</b>
<b>Fig. 30</b>	The thinking process prior to ordering ancillary tests.	<b>97</b>
<b>Fig. 31</b>	Ocular features of Behçet's disease.	<b>100</b>
<b>Fig.32</b>	Features of ocular sarcoidosis.	<b>102</b>
<b>Fig. 33</b>	Vogt-Koyanagi-Harada disease.	<b>106</b>
<b>Fig. 34</b>	Features of sympathetic ophthalmia.	<b>108</b>
<b>Fig.35</b>	Retinal features in SLE.	<b>109</b>
<b>Fig. 36</b>	ICG of serpiginous choroidopathy .	<b>112</b>
<b>Fig. 37</b>	Birdshot choroidopathy.	<b>114</b>
<b>Fig. 38</b>	Multifocal choroiditis.	<b>115</b>
<b>Fig. 39</b>	Patient with PIC and subretinal fibrosis.	<b>116</b>

## **List of Tables**

<b>Table 1</b>	The SUN Working Group Anatomic Classification of Uveitis	<b>9</b>
<b>Table 2</b>	Evidence of Immune Activation in Patients with Noninfectious Uveitis	<b>16</b>
<b>Table 3</b>	HLA Associations with Noninfectious Ocular Inflammatory Conditions	<b>16</b>
<b>Table 4</b>	The SUN Working Group Descriptors of Uveitis	<b>21</b>
<b>Table 5</b>	The SUN Working Group Grading Scheme for Anterior Chamber Cells and Flare	<b>21</b>
<b>Table 6</b>	Grading of Vitreous Haze Through the Binocular Indirect Ophthalmoscope (BIO SCORE)	<b>23</b>
<b>Table 7</b>	Causes and Associations of Retinal Vasculitis	<b>27</b>
<b>Table 8</b>	Commoner Causes of Periphlebitis and Arteritis	<b>28</b>
<b>Table 9</b>	Relative Contraindications of Systemically Administered Corticosteroids	<b>64</b>
<b>Table 10</b>	International Study Group Criteria for the Diagnosis of Behçet's Disease	<b>99</b>
<b>Table 11</b>	Revised Diagnostic Criteria for VKH Disease by the International Committee on Nomenclature	<b>103</b>
<b>Table 12</b>	Birdshot Chorioretinopathy Diagnostic Criteria for Research Purposes by an International Consensus Conference	<b>113</b>

## **List of boxes**

<b>Box 1</b>	Classification of the level of severity of the threat to vision in PSII	<b>53</b>
<b>Box 2</b>	Treatment of Severe Disease.....	<b>54</b>
<b>Box 3</b>	Treatment of Anterior segment sight threatening disease.....	<b>57</b>
<b>Box 4</b>	Algorithm of Two Approaches to Immunomodulation.....	<b>63</b>
<b>Box 5</b>	Commonly used immunosuppressive agents in ocular inflammatory Disease.....	<b>70</b>

## INTRODUCTION

Uveitis is defined as inflammation of the uveal tract, the vascular coat of the eye which is composed of the iris, ciliary body and choroid. Inflammation of these structures is frequently accompanied by involvement of the surrounding ocular tissues, including the cornea, sclera, vitreous, retina and optic nerve (**foster & vitale 2002**).

So the term uveitis is used clinically to describe a heterogeneous group of diseases characterised by inflammation of intraocular structures(**suhler et al,2005**)

Refractory uveitis refers to uveitis which may be progressive and debilitating despite aggressive treatment with conventional therapy ( **Bodaghi et al,2003**)

Uveitis as an inflammatory eye disease is a leading cause of blindness especially in the working age population (**Choudary et al, 2006**) & (**Fraser R et al, 2007**)

The incidence of blindness in uveitis can be as high as 35% with bilateral loss in 10% (**Choudary et al.,2006**)

Management of refractory uveitis remains a significant clinical challenge. The course is persistent, with periods of improvement and flare, leaving a significant ocular morbidity (**C-Elga Rabinovich et al.,2007**)

Systemic corticosteroids are typically used in acute stage of when local steroid therapy doesn't control the inflammation.

The long term use of systemic steroids is problematic because of its adverse side effects (**VA Shanmuganathan et al.,2005**)

This has led to the formulation of a therapeutic philosophy that calls for complete elimination of active inflammation, limited tolerance for the use of corticosteroids and the early implantation of immunomodulatory therapy (IMT), as either a steroid replacing therapy or first line treatment, when indicated, in an effort to minimize secondary side effects and to preserve visual function (**vitale et al.,2006**)

A step ladder algorithm that is steroid sparing and is titrated to the clinical picture in its aggressiveness may be used by an ophthalmologist who is experienced in the use of immunomodulatory therapy and the management of the potentially serious toxicities that may arise from using this step ladder algorithm. It is used in the following order:

1-Initial treatment with corticosteroids.

2-Systemic non-steroidal anti-inflammatory medications for selected indications.

3-Systemic immunomodulatory therapy(IMT)as:

a-Anti-metabolites e.g.:methotrexate and azathioprine.

b-T-cell signal transduction inhibitors as cyclosporine.

c-Alkylating agents e.g.:chlorambucil

d-Intravenous immunoglobulins.

e-Biologic agents:Interferonalpha, Infliximab, Etanercept, Daclizumab and Anakinra.

4-Peripheral retinopathy or laser photocoagulation in certain patients with intermediate Uveitis and parsplanitis.

5-Surgical treatment of uveitis and therapeutic parsplana vitrectomy.

6-Surgical treatment of complications of uveitis (**vitale et al.,2006**)

### **Contents:**

-Uveal tract anatomy and physiology.

-Epidemiology and pathology of refractory uveitis

-Classification and diagnosis of uveitis

-Treatment of refractory uveitis

-Work up for specific disease entities

### **AIM OF THE WORK:**

This essay aims to review the literatures concerned with the recent trends in management of refractory uveitis.

## ANATOMY OF THE UVEAL TRACT

### INTRODUCTION

The uvea (from the Latin *uva*, meaning grape) is a pigmented structure that primarily lies between the retina and the sclera and constitutes the vascular portion of the eye. Its blood supply comes from the ophthalmic artery, which nourishes most of the eye through branches of the anterior and posterior ciliary arteries. A separate branch of the ophthalmic artery, the central retinal artery, supplies the inner retinal layers and part of the optic nerve. The uvea also has secretory and mechanical functions including production of aqueous humor, improvement of aqueous outflow, and control of near accommodation. The uvea may become involved in disease processes through inflammation, known as uveitis, neoplasia (e.g., melanoma), and growth of abnormal vessels, known as choroidal neovascularization. (Yanoff,2004)

### IRIS

The anterior portion of the uvea is called the iris . It is composed primarily of vascular stroma as well as melanocytes, nerves, clump cells, collagen, and hyaluronidase-sensitive acid mucopolysaccharides. The vascular supply to the iris originates in the anterior and long posterior ciliary branches of the ophthalmic artery. These branches join in the ciliary body to form the major arterial circle before entering radially into the iris. The vessels lack an internal elastic lamina and are lined by nonfenestrated endothelial cells.(FINE BS, YANOFF M,1972)

The anterior surface of the iris is composed of a fibroblast cell layer folded into many ridges and crypts, with a pupillary aperture located slightly inferonasal to the center.( Hogan MJ, Alvarado JA,1971). Eye color is determined by the number and degree of melanin granules in the stromal melanocytes (Apple DJ, Rabb MF,1992)

Muscular and pigment epithelial structures are located in the posterior portion of the iris. Smooth muscle is tightly arranged in a circle to form the pupillary sphincter and is primarily innervated by parasympathetic nerves coming from the third cranial nerve nucleus. The radially oriented dilator muscles extend from their cell bodies in the anterior pigment