IMMUNOMODULATORY THERAPY FOR NON-INFECTIOUS UVEITIS

Essay
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Praise be to ALLAH, Almighty, the All-Kind and All-Merciful and peace and blessings be upon HIS messenger, Mohammad.

قال الله تعالى:

”ولو كان من عند غير الله لوجدوا فيه

اختلافا كثيرا“

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Dedication

*My deepest love, appreciation and gratefulness are to my father, Dr. **Saad Mahmoud Hanout**, who stands behind every achievement I accomplish in this career.*

I would like to show love and thankfulness to my dear beloved mother, my dear beloved wife and my sweetheart daughters for their encouragement, help and support that enabled me to achieve this work.

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List of Abbreviations

AAU	**:**	Acute Anterior Uveitis
AC	**:**	Anterior Chamber
ANA	**:**	Anti Nuclear Antibody
APCs	**:**	Antigen Presenting Cells
APMPPE	**:**	Acute Posterior Multifocal Placoid Pigment Epitheliopathy
AS	**:**	Ankylosing Spondylitis
AZOOR	**:**	Acute Zonal Occult Outer Retinopathy
CD4+/8+	**:**	Cluster of Differentiation 4+/8+
CME	**:**	Cystoid Macular Edema
CMV	**:**	Cytomegalovirus
CNV	**:**	Choroidal Neovascularization
CsA	**:**	Cyclosporin
FHI	**:**	Fuch's Heterochromic Iridocyclitis
GCC	**:**	Glaucomatocyclitic Crisis
HLA	**:**	Human Leukocytic Antigen
IFN	**:**	Interferon
IL	**:**	Interleukin
IMT	**:**	Immunomodulatory Therapy
IU	**:**	Intermediate Uveitis
JIA	**:**	Juvenile Idiopathic Arthritis
JRA	**:**	Juvenile Rheumatoid Arthritis
LFTs	**:**	Liver Function Tests

MAC	**:**	M-avium complex
MEWDS	**:**	Multiple Evanescent White Dot Syndrome
MIF	**:**	Migration Inhibition Factor
MMF	**:**	Mycophenolate Mofetil
MS	**:**	Multiple Sclerosis
NSAIDs	**:**	Non Steroidal Anti Inflammatory Drugs
PAN	**:**	PolyArteritis Nodosa
PSS	**:**	Posner Schlossman Syndrome
RPE	**:**	Retinal Pigment Epithelium
SLE	**:**	Systemic Lupus Erythematosis
SO	**:**	Sympathetic Ophthalmitis
TCRs	**:**	T Cell Receptors
TNF	**:**	Tumour Necrosis Factor
TPMT	**:**	Thiopurine S-Methyl Transferrase
VKHS	**:**	Vogt – Koyanagi - Harada Syndrome

Introduction

Uveitis by strict definition implies an inflammation of the uveal tract. However, the term is now used to describe many forms of intraocular inflammation involving not only the uveal tract but also the retina and its vessels ***(Jabs et al., 2005).***

It is a significant cause of visual impairment, accounting for up to 15% of blindness worldwide. Chronic, active, even low-grade inflammation produces irreversible damage to ocular structures such as the macula, optic nerve, and ciliary body, which are critical for good vision ***(Vitale and Smith, 2006).***

The causes of uveitis can be infectious, traumatic, toxic, metabolic, neoplastic or autoimmune (***Opremcak et al., 2006***). In the majority of patients, the cause of uveitis remain obscure even after extensive investigations. However, in good percentage of cases the underlying mechanisms appear to be autoimmune ***(Geeta and Narsing, 2004).***

Immunosuppressive treatment in the form of systemic and/or local therapy is often required**.** Corticosteroids are the mainstay of therapy for ocular inflammatory diseases and can be given by a variety of routes ***(Wilner and Lightman, 2009).***

Although corticosteroids remain the main stay and the first line of treatment for chronic noninfectious uveitis, chronic

administration of systemic corticosteroids is associated with numerous adverse side effects that are unacceptable to both the physician and the patient. This has lead to the formulation of a therapeutic philosophy that calls for early emplementation of immunomodulatory therapy as either a steroid sparing therapy or first line treatment, when indicated, in an effort to minimize secondary side effects and to preserve visual function ***(Vitale and Smith, 2006).***

The choice of treatment for noninfectious inflammatory uveitis depends on several factors. The diagnosis, the severity of the disease, the presence of concurrent systemic disease requiring immunosuppression, the duration of inflammation, the reversibility of visual loss and whether it is unilateral or bilateral are the main indicators. Other factors that need to be considered when choosing treatments are due to drug-related side effects and interactions, including the general health of the patient (e.g., the presence of diabetes, renal failure, liver dysfunction and hypertension), and patient compliance to medication and follow-up. There have been changes in the management of uveitis over the last few years, with immunomodulatory agents and new intraocular delivery systems ***(Fraser and Pavesio, 2008).***

Aim of the work

The purpose of this essay is to summarize the current concepts and recent literature regarding the use of immunosuppressive and different immunomodulatory agents available in treating noninfectious uveitis.

Anatomy of The Uveal Tract

The Uvea (from the Latin ***Uva,*** meaning grape) is the pigmented vascular middle layer of the eye lying between the corneosclera and the neuroepithelium. It consists of three main parts: the iris anteriorly, the ciliary body in the middle, and the choroid posteriorly ***(Fine and Yanoff, 1972)***.

The Iris:

Is the anterior portion of the *Uvea* consisting of vascular stroma , muscles, melanocytes, nerves, clump cells, and mucopolysaccharides ***[Fig. 1] (Fine and Yanoff, 1972).***

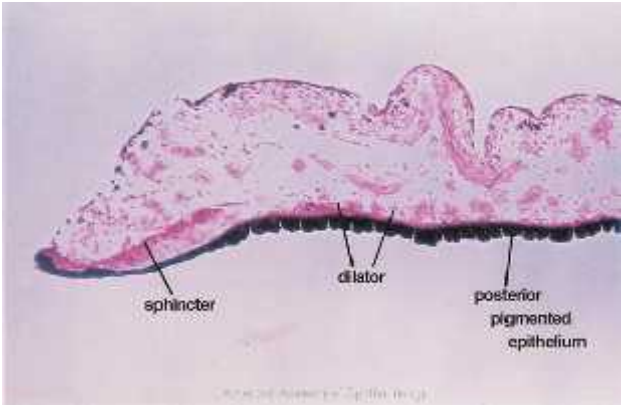

Fig. 1: Normal iris (Weingeist, 2009).

The vascular supply to the iris originates in the anterior and long posterior ciliary arteries; and join in the ciliary body to form the major arterial circle before radiating into the iris to form the minor arterial circle. They lack an internal elastic lamina and are lined by non-fenestrated endothelial cells (***Park, 2004***).

The anterior surface of the iris is folded into many ridges and crypts, with a pupillary aperture located slightly inferonasal to the center **(*Hogan et al., 1971*)**. The eye colour is determined by the number and degree of melanin granules in the stromal melanocytes (***Apple and Rabb, 1991***).

The pupillary sphincter is formed of smooth muscles which are tightly arranged in a circle and receives parasympathetic supply from the third cranial nerve nucleus. The radially oriented dilator muscles extend from their cell bodies in the anterior pigment epithelial layer and are innervated by the sympathetic nervous system (***Park, 2004***).

The posterior iris epithelium is velvety smooth; with pigmented columnar cells arranged apex to apex in two layers, absorbing incident light that does not enter through the pupil and are continuous with the pigmented and non-pigmented layers of the ciliary body epithelium ***(Kardon, 1995)***.

The Ciliary Body:

The anterior portion of the ciliary body, ***the pars plicata*** , is composed of approximately 70 ciliary processes ***[Fig. 2].***

Fig. 2: The Anterior Chamber Angle: *Note the triangular shape of ciliary body & the ciliary procsses* ***(Weingeist, 2009).***

The ciliary processes are radially arranged and consists of vascularized stromal cores surrounded by two layers of epithelium, the outer pigmented and the inner non-pigmented layers. The cells of these two layers are arranged apex to apex with tight junctions between them ***(Green, 1996).***

The zonula occludens near the apices of the non-pigmented epithelial cells form the blood-aqueous barrier. These cells are also the site of aqueous secretion; which is influenced by the rate of the ciliary body blood flow (***Park, 2004***).

The posterior portion of the ciliary body, ***the pars plana***, is a flat structure, 4 mm in length, located between the pars plicata and the ora serrata ***(Aiello et al., 1992)***.

The outer layer of the pars plana is composed of pigmented epithelial cells that are continuous with the retinal pigment epithelium, while the inner layer is made up of non-pigmented