نموذج طلب دعم مشروع بحثي

رقم البحث:

عنوان البحث : فعاليه استخدام (مايكوفينوليت موفيتيل) كعلاج لالتهابات العين العنبيه وقدرته على تقليل جرعه الكورتيزون المستخدمه في علاجها.

الباحث الرئيس والقسم الذي ينتمي إليه : معن الخراشي– قسم العيون– كلية الطب
الباحثون المشاركون والأقسام التي ينتمون إليها : حسب القائمة في صفحة رقم 3

مدة البحث : 7 أشهر **الميزانية المقترحة: لا يحتاج**

ملخص البحث (ما بين 150–200 كلمة)

- **مشكلة البحث :–**

تشكل الالتهابات العنبيه للعين مشكله كبيره للمرضى الذين يعانون منها اذ انها من الامراض المزمنه والمتكرره تؤدي الى العمى و تحتاج في علاجها الى جرعات من الكورتيزون مما يعرضهم الى اثارها الجانبيه الكثيره بالاضافه الا عدم قدرتها بالتحكم في المرض بشكل جيد ومقنع.

- **أهمية البحث :–**

ان ايجاد بدائل علاجيه لمثل هذه الحالات قد يشكل نقله نوعيه في حياه المريض واستجابته للدواء المعطى مما يعمل على تحسين حالته الصحيه بالاضافه الى تجنيبه العديد من الاثار الجانبيه العديده الناجمه من استخدام الكورتيزون كعلاج اساسي لمثل هذه الالتهابات.

❖ **أهداف البحث :–**

- معرفة فعاليه "المايكوفينوليت موفيتيل" في علاج التهابات العين العنبيه.
- التحقق من قدرة هذا الدواء في تقليل جرعه الكورتيزون المستخدمه وامكانيه التوقف من استخدامه كلياً.

❖ **منهجية البحث :–**

بعد الحصول على الموافقة سوف نقوم بجمع ملفات المرضى اللذين يعانون من هذا المرض ويستخدمون العلاج المعني ومراجعة سجلاتهم الطبيه لمعرفه مدى التغيرات التي حصلت في حالتهم المرضيه بعد استخدام الدواء ومعرفه جرعات الكورتيزون التي كانو يستخدمونها قبل وبعد بدأ العلاج بالمايكوفينوليت موفيتل

توقيع الباحث الرئيس : التاريخ :

ملاحظة: لا يقبل أي ملخص ما لم يقدم مطبوعاً باللغة العربية و موقعاً من الباحث الرئيس.

*Please, fill this page if the research proposal is submitted in **English**.*

Research Title:

The efficacy of Mycophenolate Mofetill in the treatment of Uveitis and its ability to taper the dose of steroid.

Summary: (150 – 200 words)

❖ **Research Problem:**

Uveitis is a major health problem in the patients who suffer from this condition as it is a chronic, recurrent disease and a major cause of blindness that needs a continues use of steroid in controlling the condition which expose the patient to the endless list of side effects of steroid yet not having a satisfactory results in controlling the disease.

❖ **Research Significance:**

The presence of another effective and safe medication for treating this disease will help the patients in controlling their condition and spare them the wide variety of steroid side effects.

❖ **Research Objectives:**

1. To find out the efficacy of using mycophenolate mofetill in treating uveitis.
2. To determine the ability of mycophenolate mofetill to taper the dose of steroid used and the ability to stop using them at all.
3. To find out the tolerability of mycophenolate mofetil and possible side effects.

❖ **Research Methodology:**

We will retrospectively review the medical records of patients with uveitis who use MMP as steroid sparing agents. Data collection will include demography, types of uveitis, dose of steroids before and after starting MMP, grade of inflammation before and after starting MMP.

مقترح مشروع بحثي

Research Project Proposal

Please, type either in English or Arabic — *فضلاً، تتم الطباعة إما باللغة العربية أو الإنجليزية*

التوقيع Signature	الكلية/القسم College/Department	الرتبة العلمية Academic Title	أسماء الباحثين* *Investigators Names
	الطب	طبيب إمتياز	معن بن سليمان الخراشي
	الطب – قسم العيون	أستاذ مساعد	عبدالرحمن بن محمد المعمر
	الطب – قسم العيون	أستاذ	أحمد مختار أبو الأسرار

** الاسم الأول: الباحث الرئيس.*

الاسم الثاني: الباحث المشارك الذي يرشحه الباحث الرئيس ليتولى القيام بالبحث في حال تغيب الباحث الرئيس أو تخليه عن البحث.

* *First name indicates the Principal Investigator (PI).*
Second name is the co-investigator designated by the PI to assume all responsibilities, in case of the absence of the PI.

مشكلة البحث و أهميته

Research Problem and Significance

Research problem:

Uveitis is defined as inflammation of one or all parts of the uveal tract. Components of the uveal tract include the iris, the ciliary body, and the choroid. Uveitis may involve all areas of the uveal tract or just be confined to part of it [9]. The most widely used classification of uveitis is the one devised by the International Uveitis Study Group (IUSG) in 1987, based on the anatomical location of the inflammation. This classification includes anterior uveitis (iritis, iridocyclitis, and anterior cyclitis), intermediate uveitis (para planitis, posterior cyclitis, and hyalitis), and posterior uveitis (focal, multifocal, or diffuse choroiditis, chorioretinitis, retinitis, and neuroretinitis). An additional term, panuveitis (anterior chamber, vitreous, retina, and choroid), is also described [11]. The exact pathophysiology of uveitis is unknown. In general, uveitis is caused by an immune reaction. Uveitis is usually idiopathic but often associated with infections, such as herpes, toxoplasmosis, and syphilis; therefore, the postulated immune reaction directed against foreign molecules or antigens also may injure the uveal tract vessels and cells. Uveitis also is found in association with autoimmune disorders, such as ankylosing spondylitis, inflammatory bowel disease, Reiter syndrome, psoriatic arthritis, and Behçet disease. In these cases, uveitis may be caused by a hypersensitivity reaction involving immune complex deposition within the uveal tract. The estimated international incidence is approximately 15 cases per 100,000 persons with the majority of patients aged 20-50 years [9].

In the acute presentation of the disease the patients usually suffer from photophobia with redness and ocular pain and decreased visual acuity. In examination there are usually signs of inflammation anterior chamber cells and flares, occasional keratitic precipitates and hypopyon in the severe cases.

Treatment of uveitis has been always a problem to ophthalmologists, apart from treating the underlying cause (if any) and the symptomatic treatment, the main objective is to treat the inflammatory response and this task is usually carried out by the use of steroid or other immunosuppressive drugs. Although prednisone usually is effective for controlling ocular inflammation, dose related prednisone side effects such as hypertension, hyperglycemia, diabetes, hypercholesterolemia, osteoporosis and aseptic necrosis of bone, necessitate targeting daily doses of prednisone to < 10 mg when the drug is needed on a chronic basis [2].

Mycophenolate mofetill (CellCept) is an immunosuppressive drug that has been wildly used in the treatment of renal transplant rejection, then it was introduced to treat many autoimmune diseases such as haemolytic anemia, rheumatoid arthritis, pemphigoid vulgaris, SLE and Crohns disease[1]. Its function is mainly to suppress the immune system by reversibly inhibiting inosine-5-monophosphate dehydrogenase in the purine synthesis pathway. Because mycophenolate mofetill does not affect the

salvage pathway of purine nucleotide synthesis, the inhibition results in a selective inhibition of replication of T and B lymphocytes; therefore, mycophenolate mofetill may have fewer side effects than other antimetabolites such as azathioprine [2]. Mycophenolate mofetill has been reported to be effective in experimental autoimmune uveitis in the rat [12], and it has been suggested that it may be effective for human ocular inflammatory disease as well. [1-7]

Research significance:

Uveitis is a substantial cause of ocular morbidity and vision loss. A recent review has suggested that the prevalence of blindness due to uveitis may be as high as 20%, with the majority of patients affected being in the working age group.[2] In the severe cases of ocular inflammation, chronic oral corticosteroid therapy, usually prednisone, is used to control the inflammation and prevent sight-threatening ocular complications. To spare the patients from the side effects of steroids, the usage of corticosteroid-sparing immunosuppressive or immunomodulatory drugs is usually recommended. Several immunosuppressive drugs have been reported as possibly effective in treating uveitis and to spare the usage of steroid, however, each drug has its potential side effects [10]. Because not all patients respond to any one drug, and because treatment must be individualized, an additional immunosuppressive drug that is effective in controlling the disease with a low side effect profile would be a welcome addition to the field.

أهداف البحث

Research Objectives

The goals of this project will be to:

- Find out the efficacy of using mycophenolate mofetill in treating uveitis.
- Determine the ability of mycophenolate mofetill to taper the dose of steroid used and the ability to stop using them at all.
- Find out the tolerability of MMP and possible side effects

منهجية البحث

Research Methodology

- Retrospective cohort chart review of patients with uveitis and using mycophenolate mofetill.

Mycophenolate Mofetil (MMF) is a salt form of the immunosuppressive drug mycophenolic acid. The salt form is much better tolerated and allows good and rapid absorption by the body before it is converted to the active agent mycophenolic acid.

Mycophenolate mofetil is hydrolyzed to form mycophenolic acid (MPA), which is the active metabolite. MPA is a potent, selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines, whereas other cell types can utilize salvage pathways, MPA has potent cytostatic effects on lymphocytes. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. Addition of guanosine or deoxyguanosine reverses the cytostatic effects of MPA on lymphocytes. MPA also suppresses antibody formation by B-lymphocytes. MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection. Mycophenolate mofetil did not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but did block the coupling of these events to DNA synthesis and proliferation.

Mycophenolate Mofetil was first used in the 1970s for the treatment of psoriasis, since the mid-1990s the greatest clinical experience has been with MMF in renal allograft transplantation, where it is now of established efficacy [1]. The drug has also been used successfully for the treatment of bullous pemphigoid, pemphigus vulgaris, ocular pemphigoid, rheumatoid arthritis, autoimmune hemolytic anemia, systemic lupus erythematosus and crohn's disease [1]. MMF has been shown to inhibit experimental autoimmune uveitis in rats [12].

High doses of prednisolone alone or in combination with immunosuppressive agents such as cyclosporine A (CsA), and methotrexate (MTX) are often required to control the sight-threatening and sometimes blinding consequences of intraocular inflammation. However, up to a third of patients may fail on this regime, and CsA and prednisolone both bear a considerable long-term risk due to their toxic effects on protein and glucose metabolism and on the kidney [1].

The efficacy of using MMF in the treatment of intraocular inflammation has been determined in few studies and gave promising results [4-7]. Siepmann et al [1], found that MMP (1g twice daily) was effective in controlling intraocular inflammation as well as achieving prednisolone reduction in 102 patients out of 106 patients with uveitis. MMP had limited side effects such as gastrointestinal upset

(15%), headache (9.3%), fatigue (57%), eczema (5%), and hair loss (3.5%) . Galor et al [3], found that MMP was successful in controlling ocular inflammation and tapering prednisolone dose to ≤ 10mg daily in 79% of 129 patients with ocular inflammation. Thorne et al [2], found MMP to be effective in controlling inflammation and tapering prednisolone ≤ 10 mg in 82% of 84 patients. The most frequent side effect was gastrointestinal upset and 7 patients (8.3%) had to discontinue MMP due to side effect.

المراجع

References

1. Siepmann K, et al., Mycophenolate mofetill *in a highly effective and safe immunosuppressive agent for the treatment of uveitis: aretrospective analysis of 106 patients...*Graefe's Arch Clin Exp Ophthalmol (2006) 244: 788-794.
2. Jennifer E. Thorne,et al. Mycophenolate mofetill *therapy for inlammatory eye disease. Ophthalmology (2005) 112: 1472-77*
3. Anat Galor, et al, *Comparison of antimetabolite drugs as corticosteroid-sparing therapy for noninfectious ocular inflammation. Ophthalmology (2005) 115: 1826-32.*
4. Chun H Lau, et al., Long term efficacy of Mycophenolate mofetill in the control of severe intraocular inflammation. Clinical and experimental ophthalmology (2003) 31: 487-491
5. K. Greiner, et al. Efficacy of Mycophenolate mofetill in the treatment of intermediate and posterior uveitis. Der Ophthalmology (2002) 9 : 691-94.
6. M R Wilkins et al. Mycophenolate mofetill for the treatment of severe inflammatory external eye disease. Br J Ophthalmol (2008) 92: 578-79.
7. Llinares-Tello F,et al. Monitoring trough plasma concentration of Mycophenolate mofetill in patient with uveitis.
8. D Doycheva , et al. Mycophenolate mofetill in the treatment of uveitis in children. Br J Ophthalmol (2007) 91: 180-84
9. Kilbourn Gordon. iritis and uveitis**,** Urgent Care Physician, Primary Medical, Huntington Walk-In and Greenwich Convenient Medical Center, http://emedicine.medscape.com/article/798323-overview
10. Jabs DA, et al. guide lines for the use of immunosuppressive drugs in patients with inflammatory disorders. Am J Ophthalmol (2000) 130: 492-513
11. Saadia Zohra Farooqui, C Stephen Foster**,** Uveitis, Classification. Harvard Medical School, Department of Ophthalmology, Ocular Immunology and Uveitis Foundation, http://emedicine .medscape.com/article/1208936-overview
12. Chanaud NP, et al. Inhibition of experimental autoimmune uveoretinitis by mycophenolate mofetill. Exp Eye Res (1995) 61: 429-34

الميزانية التفصيلية

Detailed Budget

المبلغ المطلوب Funds in SR	Details التفاصيل	
	مقدار الجهد بالشهر Effort in months	أسماء الباحثين Names of Investigators
1200x(شهر)=0		(1)
1000x(شهر)= 0		(2)
1000x(شهر)= 0		(3)
1000x(شهر)=		(4)
1000x(شهر)=		(5)
Zero	مجموع البند (1) (لا يزيد عن 40% من الميزانية الإجمالية للبحث) Total(1)	

Investigators (1) — (1) الباحثون

المبلغ المطلوب Funds in SR	مقدار الجهد بالشهر Effort in months	العدد Number
		(أ) مساعد باحث ( ) ( ) a) Research Assistant ( ) ***Neurophysiology and Clinical***
		(ب) فني مختبر ( ) ( ) b) Lab Technician ( ) Blood and DNA extraction and neuropathology
		(ج) طالب جامعي ( ) ( ) c) University Students ( )
		(د) إداريون ( ) d) Secretaries (1)
		(هـ) مهارات أخرى( ) ( ) e) Other professionals ( )
zero	Total (2)	مجموع البند(2)

Assistants (2) — (2) مساعدون

zero	(أ) الأجهزة والبرمجيات a) Equipment & software

(3) مستلزمات — ments, materials and supplies

zero	*(b) Materials*	*(ب) المواد*
zero	*(c) Supplies*	*(ج) التجهيزات*
zero	*Total (3)*	*مجموع البند(3)*

(4)

zero	*Domestic travel*	*الرحلات الداخلية*

(4)

(5)

zero	*Computer services*	*خدمات الحاسب الآلي*

(5)

(6)

zero	*Other services*	*خدمات أخرى*

(6)

zero	*Grand Total*	*المجموع الكلي*

الخطة الزمنية للبحث

RESEARCH TIME SCHEDULE

starting Date : / / H.

تاريخ بداية البحث: / / 142 هـ

Items البند	التوالي المخطط للأعمال الرئيسة Planned sequence of major tasks	First Year السنة الأولى												Second Year السنة الثانية											
		1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
1	Literature collection and updating;	x	x																						
2	Collection of appropriate patients charts			x																					
3	Reviewing patients charts				x	x																			
4	Data analysis						x																		
5	Final reports							x																	

إتـــفـــاقيـــة مـــلـــزمـــة

Obligatory Agreement

The Principal Investigator (PI) should strictly adhere to and fulfill the following mandatory requirements concerning this research project:	يتقيد الباحث الرئيس بمتطلبات البحث التالية و يستوفيها بدقة:
1. The proposed research project has not been previously (or will not be) submitted, either fully or partially, to any other institution.	1. لم يقدم و لن يتم تقديم مقترح هذا البحث كلياً أو جزئياً إلى أيّ جهة بحثية أخرى.
2. The stated research project objectives will be achieved within the duration of research work.	2. يتم إنهاء أهداف مشروع البحث خلال مدة البحث.
3. The allocated budget and the stipulated period of the research project are planned accurately, taking all factors into consideration.	3. تم إعداد الميزانية و الخطة الزمنية للبحث بدقة ، و أخذت كافة الاعتبارات في الحسبان.
4.Progress report forms (one at the end of each semester) as well as questionnaires on the research assistant's activities (if any) will be submitted in due time.	4. يتم تسليم تقارير المتابعة و استطلاع الرأي عن مساعد الباحث (إن وجد) في موعدها مع نهاية كل فصل دراسي.
5. Scientific lectures, highlighting the results and conclusions derived, will have to be delivered. This will be arranged with the Research Center during the course of the research at suitable venue.	5. يتم تقديم محاضرات علمية بالتنسيق مع مركز البحوث، تلقي الضوء على النتائج و الخاتمة التي تم الوصول إليها.
6.The Research Center will be provided a copy of the research papers, related to the research project, published in scientific journals, conferences, etc.	6. يتم تزويد مركز البحوث بنسخة من الأوراق العلمية ذات العلاقة التي تم نشرها في المجلات و المؤتمرات العلمية ...الخ.
7. A final comprehensive research report will be submitted by the end of the research project. This report will describe the objectives of the research, literature review and the relevant theoretical background. It will also show in detail the methodologies, techniques and experimental set-up used in conducting the research, as well as the results obtained and analysis carried out. It should include conclusions and recommendations, which might be useful for practical applications.	7. يتم تسليم تقرير نهائي شامل لمركز البحوث عند نهاية البحث. يوضح التقرير أهداف البحث و المسح المرجعي و الخلفية النظرية، كما يشمل منهجية مفصلة للبحث و أساليب وتجهيز التجارب المعملية المستخدمة في البحث، إلى جانب النتائج و تحليلها. وكذلك تضمن التوصيات و النتائج التي يتوقع أن تفيد في التطبيقات العملية.

Signature (PI): _____ Date : / /142 H