United States

First-line Antimetabolites as Steroid-sparing Treatment (FAST) Uveitis Trial

The current mainstay of treatment for noninfectious uveitis is corticosteroids. However, side effects associated with long-term corticosteroid therapy necessitate the use of other immunosuppressive therapies. The two most commonly used of these therapies are methotrexate and mycophenolate mofetil. There have been no prospective randomized, controlled trials to systematically determine which antimetabolite is more clinically efficacious as initial corticosteroid-sparing therapy.

To address this gap in clinical knowledge, Dr. Acharya has designed and is coordinating the FAST study as a multi-center, block-randomized, observer-masked, comparative effectiveness trial, with the aim of establishing which drug is more effective as a first-line therapy. This large NIH-funded trial is taking place in collaboration with uveitis specialists Dr. Rathinam at Aravind Eye Hospital in India, Dr. Hassan Dhibi at King Khaled Eye Specialist Hospital in Saudi Arabia, Dr. Debra Goldstein at Northwestern University, Dr. Eric Suhler at Oregon Health Sciences University, Dr. Lourdes Arellanes at Asociacion Para Evitar la Ceguera in Mexico City, and Dr. Lyndell Lim at Royal Victorian Eye and Ear Hospital in Melbourne, Australia.

Discovering Infectious Pathogens (DIP) Uveitis Study

Dr. Acharya, in collaboration with Dr. Thuy Doan and the DeRisi Lab at UCSF, is conducting the DIP Uveitis Study to develop a new method for identifying infectious causes of uveitis, an inflammatory eye disease. There are a number of causes and conditions related to the development of uveitis, and extensive investigations are often carried out to determine if the underlying cause is infectious or autoimmune-based. To confirm an infectious cause, a small sample of fluid from inside the eye may be collected for PCR or culture. However, the PCR technique is limited in the types and quantity of pathogens it can detect. Fortunately, next generation sequencing and sophisticated bioinformatics tools are starting to revolutionize our ability to identify known and previously unidentified pathogens. This study aims to use a next generation analytical approach to identify pathogens that are not routinely tested for in a clinical setting. The DeRisi lab is a pioneer in this field and has the tools and expertise to make significant strides in finding pathogens that may be responsible for uveitis of unknown cause.

Evaluating the usefulness of the International Diagnostic Criteria for Ocular Sarcoidosis: a multi-center retrospective study

Sarcoidosis, a rare, multi-systemic chronic inflammatory disease of unknown etiology, is one of the major disease associations with uveitis, and is the leading cause of uveitis in Japan. In many cases, it is the manifestion of ocular symptoms that leads to the detection of sarcoidosis. Diagnosing sarcoidosis, however, remains extremely difficult. The gold standard for making a definitive diagnosis involves a biopsy of relevant tissue. Because biopsies are often unacceptable to patients,the clinician is often left with the task of making a diagnosis based on clinical and laboratory characteristics.

Some effort has been made to determine what clinical and laboratory signs are useful in correctly diagnosing uveitis patients with sarcoidosis. In 2009, the International Workshop on Ocular Sarcoidosis (IWOS) published a set of guidelines for characterizing uveitis patients suspected of having sarcoidosis into four diagnostic categories: definite, presumed, probable, and possible. More work is necessary to determine the validity of the guidelines proposed by the first meeting of the IWOS. Thus, Dr. Acharya is conducting a large-scale international study incorporating the diagnostic experience of 17 centers worldwide in order to generate a sufficient sample size and diverse patient population to evaluate the diagnostic utility of these guidelines.

Epidemiologic Studies on Uveitis

Dr. Acharya?s research group is studying the predictors of clinical outcomes such as visual acuity and ocular complications in subtypes of uveitis, as well as assessing clinical outcomes in patients treated with various immunomodulatory treatments, including biologic therapies. The research group is also investigating risk factors for developing ocular inflammation, including exposure to various medications and having other concurrent medical conditions. The latter studies are being conducted in conjunction with Dr. Vivien Tham (Proctor alumna) and Kaiser Permanente Hawaii.

Multicenter Uveitis Steroid Treatment Trial (MUST)

Dr. Acharya is site PI of the Multicenter Uveitis Steroid Treatment Trial (MUST), which is comparing the Retisert fluocinolone acetonide steroid implant to systemic immunosuppressive therapy for the treatment of chronic intermediate, posterior or panuveitis. This study has completed enrollment, and patients are now being followed for long-term outcomes. Dr. Acharya is serving as a protocol chair to help design future clinical trials on uveitic macular edema to be conducted with the MUST network.

PeriOcular and INTravitreal corticosteroids for uveitis macular edema (POINT) trial

Dr. Acharya is site PI of the POINT trial, which is being conducted by the MUST Research Group out of Johns Hopkins University. The objective of this trial is to evaluate the relative efficacy of three commonly used regional corticosteroids for treatment of uveitic macular edema: periocular triamcinolone acetonide injection; intravitreal triamcinolone acetonide injection; and intravitreal dexamethasone implant. The primary efficacy measure is percent change in macular thickness from baseline to two months post-injection. Participants are followed for a total of six months in order to compare the duration of treatment effects, requirement for additional injections, and adverse effects among the three treatment arms.

Mycotic Ulcer Treatment Trials (MUTT)

Infectious keratitis is a leading cause of vision loss globally. Fungal keratitis accounts for as many as half of all corneal ulcers in certain tropical regions and can be more difficult to treat than bacterial corneal ulcers, often with worse outcomes. Though natamycin is the only topical antifungal approved by the United States Food and Drug Administration for topical ophthalmic use, expert surveys indicated that the majority of corneal specialists would prefer to use voriconazole. The Mycotic Ulcer Treatment Trials (MUTT) are two separate randomized, placebo-controlled, masked clinical trials funded by the National Eye Institute (NEI) and the National Institutes of Health (NIH). In the first trial (MUTT I), we compared voriconaozle to natamycin in the treatment of filamentous fungal keratitis and found that natamycin results in improved visual outcomes. The ongoing second trial (MUTT II) compares whether the addition of oral voriconazole to topical voriconazole leads to improved outcomes for severe filamentous fungal keratitis in patients treated with natamycin. These studies are a collaboration between the F.I. Proctor Foundation at UCSF, the Aravind Eye Hospitals in Madurai, Pondicherry, Coimbatore, and Tirunelveli in India, and Dartmouth Medical School. For further information about these trials, please see:

MUTT I: http://clinicaltrials.gov/ct2/show/NCT00996736 [1]

MUTT II: http://clinicaltrials.gov/ct2/show/NCT00997035 [2]

Acanthamoeba Keratitis Studies

Acanthamoeba is a ubiquitous, free-living amoeba that can cause a painful infection of the cornea which results in scarring and blindness. Though relatively rare, the infection is frequently associated with contact lens use in developed countries and with agricultural work in less developed countries. Evidence from multiple countries indicates that the incidence of acanthamoeba keratitis is increasing. Moreover, both diagnosis and treatment can be difficult, and there is minimal evidence on which to base treatment decisions. In collaboration with Aravind Eye Hospitals in India, the UCSF Proctor Foundation is conducting these studies in order to identify optimal diagnosis and treatment methods for acanthamoeba keratitis.

Mathematical Modeling

At the Proctor Foundation we use simple mathematical models to help us understand infection transmission rates as well as the most appropriate treatment plans for trachoma, the world?s leading cause of infectious blindness. We fit parameters of stochastic epidemiological transmission models to help us understand how quickly the disease is spreading. We use this information to estimate optimal treatment plans and then later compare our predictions to the actual results in our longitudinal studies. For example here we compare annual to biannual mass antibiotic treatments in Ethiopia:

M. Melese, W. Alemayehu, T. Lakew, E. Yi, J. House, J.D. Chidambaram, Z.Zhou, V. Cevallos, K. Ray, K.C. Hong, T.C. Porco, I. Phan, A. Zaidi, B.D. Gaynor, J.P. Whitcher, T.M. Lietman. ?Comparison of annual and biannual mass antibiotic administration for elimination of infectious trachoma.? JAMA, 299, (2008), 778-784. [3]

Here we have created a simple stochastic mathematical model which helps show how treatment, coverage, population size, etc. can affect infection levels:

K.J Ray, T.C. Porco, K.C. Hong, D.C. Lee, W. Alemayehu, M. Melese, T. Lakew, E. Yi, J. House, J.D. Chidambaram, J.P. Whitcher, B.D., Gaynor & T.M Lietman. ?A rationale for continuing mass antibiotic distributions for trachoma.? BMC Infect Dis, 7 (2007), 91. [4]

There is debate whether trachoma can be eradicated or only controlled with mass distributions of oral azithromycin. The World Health Organization's goal is to control infection to a level where resulting blindness is not a public health concern. Here, we use mathematical models to assess whether more ambitious goals such as local elimination or even global eradication are possible. We fit a class of non-linear, stochastic, susceptible-infectious-susceptible (SIS) models which allow positive or negative feedback, to data, and make predictions using model averaging:

Lietman TM, Gebre T, Ayele B, Ray KJ, Maher MC, See CW, Emerson PM, Porco TC; TANA Study Group. The epidemiological dynamics of infectious trachoma may facilitate elimination. Epidemics. 2011 [5] Jun;3(2):119-24.

Links
[1] http://clinicaltrials.gov/ct2/show/NCT00996736
[2] http://clinicaltrials.gov/ct2/show/NCT00997035
[3] http://jama.jamanetwork.com/article.aspx?articleid=181486
[4] https://proctor.ucsf.edu/sites/proctor.ucsf.edu/files/wysiwyg/1471-2334-7-91.pdf
[5] https://proctor.ucsf.edu/sites/proctor.ucsf.edu/files/wysiwyg/1-s2.0-S1755436511000223-main.pdf