

CHAPTER I

INTRODUCTION

Visual impairment is a common disability. An estimated 45 million people worldwide are blind, and a further 135 million people have significant visual impairment. People in developing countries are 5-10 times more likely to go blind than those in the western world (ICEE: Annual Report, 2004). One of the major causes of blindness and visual impairment is inflammation of the inner eye, or uveitis. Various factors may induce uveitis, including physical damage, autoimmune disorders, infection, or exposure to toxins. Thus, the effective treatment of ocular inflammation requires an understanding of the disease process, as well as identification of the causes and knowledge of pharmacokinetics in drug usage (Snyder *et al.*, 1994).

Uveitis is the major cause of severe visual impairment in young and middle aged adults. It has been estimated that uveitis accounts for 10-15% of total blindness in the USA (Munoz-Fernandez *et al.*, 2006). In addition, uveitis is the cause in 10% of vision loss cases and 5-20% of legal blindness cases in developed countries (Durrani *et al.*, 2004). The prevalence of uveitis in the USA is increasing, reaching an incidence of 52.4/100,000 persons and a period prevalence of 115.3/100,000 person-years (Gritz *et al.*, 2004). However, the data are lacking concerning the frequency of uveitis in South-East Asia, and specifically in Thailand.

As in other ocular inflammations, uveitis is related to several causes, including genetic influence and infections (Wakefield *et al.*, 2005). Infections caused by various etiologies include toxoplasmosis, toxocariasis, histoplasmosis, leptospirosis, tuberculosis, syphilis, AIDS, cytomegalovirus (CMV) and other herpesviruses (herpes simplex virus type 1; HSV-1, herpes simplex virus type 2; HSV-2 and varicella zoster virus; (VZV) infections are closely related to uveitis (U.S. National Library of Medicine. NIH. Uveitis, 2006). In the developed world, toxoplasmosis is the major cause of uveitis (Durrani *et al.*, 2004). However, knowledge concerning the relationship between toxoplasmosis and uveitis in developing countries is still lacking. Review data have shown that HIV-infected patients were infected with herpes zoster virus 15-25 times compared to the normal population, and have a high risk of ocular infection. Herpes zoster ophthalmicus related retinitis is often associated with anterior uveitis (Wiafe *et al.*, 2003). In the era of HIV/AIDS, the incidence of tuberculosis is increasing and is associated with uveitis worldwide, especially in Africa, Western Pacific and Eastern Europe. Other areas plagued by high and/or increasing rates of tuberculosis (TB) include certain regions of Eastern Europe and Southeast Asia. Globally, latent TB infections are more frequent and present in one third of the world's population with 20 million cases of active TB and 8-10 million new cases diagnosed each year (WebMD LLC: 1994-2011. Tuberculosis, 2006; Gupta *et al.*, 2005). Recently, the seroprevalence of infectious agents in Thai uveitis patients showed that the antibody against *Toxoplasma gondii* was significantly higher in non-HIV uveitis population. However, antibodies for *Treponema pallidum* and *Leptospira* were observed more frequently in patients with HIV-associated retinitis.

Active tuberculosis was not found in non-HIV uveitis patients (Sirirungsi *et al.*, 2009). However, the major causes of infectious uveitis in Thailand have not been analyzed.

Uveitis of unknown cause is conventionally treated with steroids or other immunosuppressive agents and mydiatric eye drop. With long term treatment of steroids, patients potentially develop many serious side effects such as moon face, cataracts, obesity, psychosis, osteoporosis, impeding growth in children, increased pressure in the eye, skin capillary fragility and increase risk of infection (Snyder *et al.*, 1994; Jabs *et al.*, 2000). Ocular inflammation is not only associated with visual disability but also with the frequent presence of systemic diseases that also increase morbidity. Moreover, these illness complications may lead to the potentially serious economic consequences with many days off work or job losses. An accurate etiological diagnosis is important for the effective treatment. Thus, it is essential to perform the diagnosis of infectious organism which causes the intraocular infection before the steroid or immunosuppressive therapy is given. The specific antibiotic treatment will provide benefits for patients both in effective treatment and decrease of the side effects of the conventional treatment with steroids or immunosuppressive drugs.

The purpose of this study is purposed to investigate the major causes of uveitis in Northern-Thai population and setting up the suitable panel for laboratory diagnosis. Major causes of infectious uveitis which were described in other parts of the world were investigated in Northern-Thai patients. Real-time PCR, a molecular technique with high sensitivity and specificity, was used to identify various causative agents in ocular fluid using the reference singleplex real-time PCR technique (de Groot-Mijnes *et al.*, 2006). Then, the multiplex real-time PCR was developed to minimize the

expense of diagnostic tests. In addition to real-time PCR analysis, Goldmann-Witmer Coefficient (GWC) analysis has been reported to improve the diagnostic efficiency. The GWC analysis which is a technique for determination of active intraocular antibody production and was together with real-time PCR analyzed. After all these experiments, we proposed the most suitable panel of diagnostic tests for Northern-Thai patients.

1. Objectives of the study

- To investigate the major causes of infectious uveitis in Northern-Thai population.
- To develop multiplex real-time PCR technique to identify organisms involved in uveitis.
- To analyse the diagnostic efficiency of Goldmann-Witmer coefficient analysis and Real-time PCR technique in identifying the causes of uveitis.

2. Education and application advantages

A. Expected results and Benefits

- The evidence of potential infectious organisms which are associated with uveitis in the Northern part of Thailand.
- To develop the effective, accurate and economically suitable laboratory methods for diagnosis of uveitis and other ocular infections.

B. Impacts

- These results would provide the additional information for the ophthalmologists in establishing the correct diagnosis, treatment and management of uveitis. This correct laboratory diagnosis provides effective treatment, minimizes a chance of severe complications and decreases the number of hospital visits which will improve in turn, economical value.
- The results of this study could be used to establish the center for diagnosis of ocular infections under the Faculty of Associated Medical Science, Chiang Mai University.
- The results of this study will be published in the scientific journals aiming to report on the incidence of the major causes of infectious uveitis in the Northern-Thai population, the multiplex real-time PCR development to identify organisms that are involved in infectious uveitis, and will determine the effective value of GWC and real-time PCR technique in identifying the causes of infectious uveitis.