Neopterin, a promising biomarker for the diagnosis of intraocular inflammation

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We reviewed studies on the role of neopterin as a biomarker of various infectious and non-infectious diseases and presented the benefits of measuring the levels of this biomarker in biological fluids in disorders involving cell-mediated immunity. The results of relevant studies in multiple fields of medicine are desctibed herein. Measuring neoptherin levels in biological fluids may be beneficial not only for diagnosis or verification of a particular disease, but also for differentiation of the disease from others resembling it, assessment of treatment efficacy and prediction of subsequent disease course.

Keywords:
neoptherin, biomarker of inflammation, cell-mediated immunity, biological fluid

The problem of uveitis is still a problem of significant proportions. The importance of the disease is determined by its prevalence, chronic recurrent course, numerous potential complications and a high rate of certified visual disability among patients with the disease [1-4]. Uveitis is estimated to be the cause of 5–10% of blindness or visual impairment worldwide [5]. In addition, 35% of patients with uveitis have significantly reduced vision [6, 7].

Endogenous uveitis can be associated with a number of systemic and local pathologic conditions and has various clinical forms [8-10]. Moreover, the disease can develop as a complication of penetrating eye injury [11] or eye surgery [12]. There has been a British report which implicated minor ocular trauma in precipitating a first episode of uveitis associated with high serum angiotensin-converting enzyme in two cases [13].

In recent decades, researchers have been trying to detect and isolate the major immune mediators responsible for key components of uveitis and characterizing the severity of inflammation [14-16]. The pro-inflammatory cytokines interleukin-1 (IL-1), IL-2, IL-4, IL-5, IL-6 and IL-10, interferon gamma (IFNγ), tumor necrosis factor-α (TNFα), and transforming growth factor have all been detected within the ocular fluids or tissues in the inflamed eye. In addition, it has been demonstrated that the chemokines, IL-8, monocyte chemoattractant protein (MCP-1), fractalkine, and macrophage inflammatory protein (MIP)1ß and MIP1γ are involved in intraocular inflammation [17, 18]. However, clinical forms of uveitis differ in cytokine-and-chemokine profiles [19]. Moreover, active cytokine interaction is essential for full immune response. Usually, the biological effect of a single cytokine is a portion of the combination effect of different cytokines [20].

It is important that concentrations of individual cytokines in biological fluids reflect only limited understanding of their interaction with immunocompetent cells, and cytokine concentrations in available biological media do not always reliably reflect a real picture of the inflammatory process. In this connection, measurements of more inert released biologically active substances are of special interest for assessing cell-mediated immunity response. Because neopterin is a biologically stable metabolite, neopterin measurements in serum, plasma, urine, and, possibly, tear fluid may be used for this purpose [21]. Neopterin is a purine nucleotide which serves as a precursor in the biosynthesis of biopterin [22, 23]. It is produced mainly by monocytes, macrophages, dendritic cells, and endothelial cells after stimulation by interferon-γ [17, 22, 24-28]. The amount of synthesized neopterin is directly proportional to the amount of IFN-γ, and also indirectly indicates an increase in TNF-α. A direct relationship has been demonstrated between neopterin hyperproduction and activating effect of these cytokines on the immune cell metabolism. In addition, neopterin has a role in the mechanism of cytotoxic effect of activated macrophages. That is, neopterin levels reflect the interplay of different cytokines for the population of monocytes/macrophages [20, 29]. As neopterin measurements allow

for identifying the activation of the cellular immune system, many have reported that neopterin is a major biomarker of numerous disorders [23, 30, 31]. It can be easily measured in serum, plasma, urine or other body fluids [23, 32-34]. The clinical value of neopterin levels in biological fluids have been investigated since the end of the last century. Serum neopterin levels > 10 nmol/l are considered elevated. Neopterin concentrations have been reported to be significantly higher in patients with elevated body mass indices and elevated glucose concentrations [35-38].

A difference in the pattern of immune response causes a difference in neopterin levels between various infectious and autoimmune disorders. Neopterin concentrations in body fluids are elevated in viral disorders, and either insignificantly increased or low in bacterial diseases due to the mostly humoral immune response. This fact may help differentiate between viral and bacterial processes [39-42]. Since the antibacterial immune response is associated with other immunity mechanisms (synthesis of antibodies, acute phase response, etc.), no significant synthesis of neopterin occurs in the presence of numerous bacterial infections. However, in the acute phase of cellular (viral, Rickettsial, Chlamydial, and etc.) infection, the cell-mediated immunity is induced, and only subsequently the humoral immunity becomes involved. This difference in the pattern of immune response causes a difference in neopterin levels in body fluids between various types of infection.

Neopterin levels in body fluids may be utilized in clinical practice not only to predict subsequent disease course [43-48], but also to assess to what extent the therapy was helpful [49-51].

There have been studies on the role of neopterin levels in various disorders. Thus, elevated neopterin levels indicate rapidly growing tumors and disseminated cancer cells with an unvavorable prognosis in cancer patients [52-55]. In addition, elevated neopterin levels have been found to be of high prognostic value for the prediction of rapid malignant transformation and mortality in cancer patients [52-56].

Numerous studies reported on the relationships between neopterin levels and myocardial lesions in ischemic cardiac disease, acute myocardial infarction, and atherosclerosis of aorta and atherosclerosis of peripheral vessels [17, 57-59].

Morover, elevated neopterin levels have been implicated in the active stage, exacerbation or progression of autoimmune diseases like rheumatoid arthritis, systemic lupus erythematosus, psoriasis, antiphospholipid syndrome, and etc. [28, 60-65].

Increased neopterin concentrations in children with heart failure or cardiovascular complications after chemotherapy for acute leukemia have been the subject of interesting reports by Russian researchers. This was explained by increased synthesis of proinflammatory cytokines by immune system cells in response to hypoxia [17, 66, 67]. Other Russian researchers have reported on longitudinal changes in serum neopterin concentrations in healthy newborns and children with central nervous system lesions. Healthy newborns were found to exhibit increased serum neopterin concentrations due to transitory immune deificiency. Stress-induced activation of macrophages and monocytes occurs in newborns during labor and is indicated by increased serum neopterin [28, 68, 69].

There have been reports on the role of neopterin in such viral infections as acute viral hepatitis, rubella, cytomegalovirus, Epstein-Barr virus, Dengue, herpes, influenza, B19 parvovirus infection, viral gut infection, tuberculosis, brucellosis, and leishmaniasis, as well as bacterial infections [45, 46, 50, 70-77]. Much attention has been given to determining the level of this biomarker in human immunodeficiency virus infection [44, 47, 51]. Interestingly, it has been demonstrated that neopterin levels were increased before the clinical symptoms appeared and before the virus and specific antibodies were detected in blood [78-79].

The success of transplantation can be partially predicted by increased neopterin levels, which reflects activation of macrophages as a result of triggering the non-specific body defence in response to tissue rejection and the concomitant inflammatory response [66, 80, 81].

Initial pre-eclampsia can be predicted by the levels of neopterin, C-reactive protein and other markers [82-84]. Recently, an interesting case-control study has been performed to assess whether neopterin and anti-Mullerian hormone can be used as markers in the condition of unexplained recurrent pregnancy loss [85]. Those authors believe that recurrent pregnancy loss can be caused by an autoimmune pathology of which the affected person was not previously aware, and this can be predicted and verified by neopterin levels. Another possible cause of recurrent pregnancy loss is an infection causing subclinical endometriosis.

Isolated reports on increased serum or urine neopterin levels in cutaneous lesions and psoriasis lesions appear [86, 87]. There have been several reports on serum or urine neopterin levels in patients with active uveitis versus uveitis in remission [88, 89]. Serif and colleagues [90] analyzed longitudinal aqueous and vitreous neopterin levels in the endotoxin-induced uveitis model. There is, however, still a need in more detailed and deeper studies on changes in the level of the biomarker in various eye disorders, effect of treatment on neopterin levels, and opportunities for predicting the course of a particular eye disease on the basis of neopterin levels.

Therefore, neopterin has been reported to be a marker of cell-mediated immunity in various diseases, with its levels reflecting the interplay of different cytokines for the population of monocytes/macrophages. The amount of synthesized neopterin is directly proportional to the amount of IFN-γ, and also directly indicates an increase in TNF-□. However, as opposed to these cytokines, neopterin is a stable metabolite, which allows for accurate

determination of its levels in biological fluids in the body. It is this that provides an opportunity to study the role of neoptherin levels not only for diagnosis or verification of a particular disease, but also for differentiation of the disease from others resembling it, as well as determination of the severity and longitudinal changes in the diseases in whose pathogenesis monocytes/macrophages play an active role. In addition, the stability of this biomarker in biological fluids may help assess the efficacy of treatment and prediction of disease recurrence and complications. These aspects, however, remain underinvestigated and warrant futher research.

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Conflict of Interest Statement:
The authors declare no conflict of interest which could influence their opinions on the subject or the materials presented in the manuscript.