Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Available online at www.sciencedirect.com

SCIENCE DIRECT

Clinical Immunology 116 (2005) 1–2

Clinical IMMUNOLOGY

www.elsevier.com/locate/yclim

Editorial

The emerging utility of neopterin?

Since neopterin was first isolated from man in 1967 [1], scientists have struggled to find mainstream utility for it measurement. It is an inherently attractive compound to invoke as a measurement of the severity of a given infection. The compound, a pteridine derivative, is produced during the metabolism of guanosine triphosphate (GTP), and monocytes and macrophages are the primary source of neopterin in humans [2]. It has therefore been regarded as a biochemical marker of cell-mediated immune response [3]. It is found in multiple body fluids including serum, urine, and cerebral spinal fluid.

Elevated neopterin levels have been demonstrated in a number of infections such as sepsis, HIV, hepatitis C, and tuberculosis [4]. The degree of elevation has been shown to be correlated with biochemical parameters such as viral load in HIV [5] and has been suggested to have some prognostic utility in sepsis, Dengue, and Ebola [6–8]. Elevated levels are not specific to infectious diseases however. Elevated levels have been documented in a variety of non-infectious states such as neoplasms, auto-immune diseases, and even pre-term labor [4].

In this issue, Zheng et al. describe elevated serum levels of neopterin in a cohort of 129 patients with SARS. The levels peak 3 days after disease onset, and higher levels were associated with more severe disease as defined by the need for mechanical ventilation and length of hospitalization. Serum neopterin levels were not elevated in convalescence, nor in healthy adults.

Could neopterin levels be utilized in the clinical management of SARS? One empyreal goal in the clinical management of SARS is to know which patients should be treated with corticosteroids. Multiple published manuscripts examining the clinical effectiveness of corticosteroids suggest that corticosteroids are beneficial in the treatment of SARS [9–18]. However, these manuscripts are all non-randomized case series and often have other methodological flaws that preclude the generation of definitive recommendations for corticosteroids.

It is unlikely that all people infected with SARS-CoV need treatment with corticosteroids. There are asymptomatic or minimally symptomatic infections with SARS-CoV that did not receive and likely do not require any corticosteroids [19]. Early treatment with corticosteroids has been shown to result in higher plasma viral loads of SARS-CoV [20], although the clinical significance of this is unclear. High dose pulsed corticosteroids may actually be associated with an increased risk of death [21]. In addition, there are significant side effects associated with corticosteroid use in SARS, such as avascular necrosis or nosocomial infections [22].

So while it is unlikely that corticosteroids are beneficial for all cases of SARS, they may be beneficial in those with the most severe disease. Consistent with this is evidence from the field of sepsis that the beneficial effects of a number of immune modifying agents including corticosteroids is related to the severity of disease [23]. The most benefit with these agents is seen patients with the highest control mortality, and detriment with these agents can be demonstrated in those with the lowest control mortality.

Early stratification for severity of disease would then be imperative. The manuscript by Zheng et al. is notable as it suggests there is test that can be performed early that accurately reflects severity of disease later in the course of infection. Other markers for severity of illness have been proposed including C reactive protein, LDH, increased age, severity of illness, lymphocyte count, neutrophil count [24,25]. However, the delineation was rarely as robust as suggested with neopterin in this manuscript. Prospective measurements of neopterin in a group of well-characterized patients infected with SARS-CoV will be necessary to validate the use of this test as a predictor of disease severity. If substantiated, neopterin may be useful to delineate a population at low risk for severe disease and therefore define a population which may not benefit from exposure to corticosteroids.

References

[1] A. Sakurai, M. Goto, Neopterin: isolation from human urine, J. Biochem. 61 (1) (1967) 142–145.

[2] I. Anwaar, A. GottsaÈter, B. Hedblad, B. Palmqvist, I. Mattiasson, F. LindgaÈrde, Endothelial derived vasoactive factors and leukocyte derived inflammatory mediators in subjects with asymptomatic atherosclerosis, Angiology 49 (1998) 957–966.

1521-6616/$ - see front matter. Published by Elsevier Inc.
doi:10.1016/j.clim.2005.03.008

[3] F.F. Hamerlinck, T. van Gool, W.R. Faber, P.A. Kager, Serum neopterin concentrations during treatment of leishmaniasis: useful as test of cure? FEMS Immunol. Med. Microbiol. 27 (2000) 31–34.
[4] A. Berdowska, K. Zwirska-Korczala, Neopterin measurement in clinical diagnosis, J. Clin. Pharm. Ther. 26 (2001) 319–329.
[5] D.S. Stein, R.H. Lyles, N.M. Graham, et al., Predicting clinical progression or death in subjects with early-stage human immunodeficiency virus (HIV) infection: a comparative analysis of quantification of HIV RNA, soluble tumor necrosis factor type II receptors, neopterin, and b2-microglobulin, J. Infect. Dis. 176 (1997) 1161–1167.
[6] G. Delogu, M.A. Casula, P. Mancini, G. Tellan, L. Signore, Serum neopterin and soluble interleukin-2 receptor for prediction of a shock state in gram-negative sepsis, J. Crit. Care 10 (2) (1995 (Jun.)) 64–71.
[7] S. Baize, E.M. Leroy, A.J. Georges, M.C. Georges-Courbot, M. Capron, I. Bedjabaga, J. Lansoud-Soukate, E. Mavoungou, Inflammatory responses in Ebola virus-infected patients, Clin. Exp. Immunol. 128 (1) (2002 (Apr.)) 163–168.
[8] K. Babb, C.V. Carrington, M.A. Monteil, A preliminary study of neopterin as a potential marker for severe dengue virus infection, Trans. R. Soc. Trop. Med. Hyg. 93 (4) (1999 (Jul.–Aug.)) 447–448.
[9] J.W.M. Chan, C.K. Ng, Y.H. Chan, et al., Short term outcome and risk factors for adverse clinical outcomes in adults with severe acute respiratory syndrome, Thorax 58 (2003) 686–689.
[10] J.J. Sung, A. Wu, G.M. Joynt, et al., Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak, Thorax 59 (2004) 414–420.
[11] K.W. Tsang, P.L. Ho, G.C. Ooi, et al., A cluster of cases of acute severe respiratory syndrome in Hong Kong, N. Engl. J. Med. 348 (2004) 1977–1985.
[12] N. Lee, D. Hui, A. Wu, et al., A major outbreak of severe acute respiratory syndrome in Hong Kong, N. Engl. J. Med. 348 (2003) 1986–1994.
[13] L.K. So, A.C. Lau, L.Y. Yam, et al., Development of a standard treatment protocol for severe acute respiratory syndrome, Lancet 361 (2003) 1615–1617.
[14] Z. Zhao, F. Zhang, M. Xu, et al., Description and early treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China, J. Med. Microbiol. 52 (2003) 715–720.
[15] J.C. Ho, G.C. Ooi, T.Y. Mok, et al., High-dose pulse versus nonpulse corticosteroid regimens in severe acute respiratory syndrome, Am. J. Respir. Crit. Care Med. 168 (2003) 1449–1456.
[16] P.T. Tsui, M.L. Kwok, H. Yuen, et al., Severe acute respiratory syndrome: clinical outcomes and prognostic correlates, Emerg. Infect. Dis. 9 (2003) 1064–1069.
[17] W. Wu, J. Wang, P. Liu, et al., A hospital outbreak of severe acute respiratory syndrome in Guangzhou, China, Chin. Med. J. 16 (2003) 811–818.
[18] N. Li, J. Ma, L. Nie, et al., Retrospective analysis of corticosteroid treatment in severe acute respiratory syndrome (SARS), Beijing Daxue Xuebao 35 (2003) 16–18 (Suppl.).
[19] K.Y. Ho, et al., Mild illness associated with severe acute respiratory syndrome coronavirus infection: lessons from a prospective seroepidemiologic study of health-care workers in a teaching hospital in Singapore, J. Infect. Dis. 189 (2004) 642–647.
[20] N. Lee, et al., Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients, J. Clin. Virol. 31 (2004) 304–309.
[21] O.T. Tsang, T.N. Chau, K.W. Choi, et al., Coronavirus-positive nasopharyngeal aspirate as predictor for severe acute respiratory syndrome mortality, Emerg. Infect. Dis. 9 (2003) 1381–1387.
[22] N. Hong, X.K. Du, Avascular necrosis of bone in severe acute respiratory syndrome, Clin. Radiol. 59 (2004) 602–608.
[23] P. Minneci, K. Deans, C. Natanson, P.Q. Eichacker, Increasing the efficacy of anti-inflammatory agents used in the treatment of sepsis, Eur. J. Clin. Microbiol. Infect. Dis. 22 (2003) 1–9.
[24] C.H. Chiang, J.F. Shih, W.J. Su, R.P. Perng, Eight-month prospective study of 14 patients with hospital-acquired severe acute respiratory syndrome, Mayo Clin. Proc. (2004 (Nov.)) 1372–1379.
[25] C.D. Gomersall, G.M. Joynt, P. Lam, T. Li, F. Yap, D. Lam, T.A. Buckley, J.J. Sung, D.S. Hui, G.E. Antonio, A.T. Ahuja, P. Leung, Short-term outcome of critically ill patients with severe acute respiratory syndrome, Intens. Care Med. 30 (3) (2004 (Mar.)) 381–387 (electronic publication 2004 Jan. 23).

John Beigel
Critical Care Medicine Department, Warren G. Magnuson, Clinical Center National Institutes of Health Building 10, 7D43 10 Center Dr., MSC 1662 Bethesda, MD 20892-1662, USA
Fax: +1 301 402 1213.
E-mail address: jbeigel@mail.nih.gov.

14 May 2005