Medical Hypotheses (2006) **66,** 855–868

ELSEVIER

medical hypotheses

http://intl.elsevierhealth.com/journals/mehy

Correspondence

Paradoxical inflammation revisited: Muraglitazar and cardiovascular risk

A recent editorial in the Journal of the American Medical Association suggests that muraglitazar, a diabetes drug under development, may be associated with an unexplained increased rate of conditions associated with inflammation such as stroke and heart disease [1]. Muraglitazar acts through the binding of peroxisome proliferator-activated receptors (PPARs), specifically the PPAR-γ family. In addition to modulating insulin sensitivity, activation of these receptors leads to an acute reduction in inflammation [2]. As we proposed earlier in the case of non-steroidal anti-inflammatory agents [3], a paradoxical host response to chronic muraglitazar use may produce compensatory increased levels of inflammation that would explain the heightened cardiovascular risk. Such paradoxical long-term sequelae have now arisen in two classes of drugs with entirely distinct mechanisms of action. This finding suggests that such effects may not necessarily arise from invoking specific functional pathways, but may originate instead from a more fundamental physiologic response — a conclusion that provides greater support for our hypothesis. Indeed, if we consider other agents with this conceptual framework in mind, we may find that this source of risk has existed and may still exist for many other medications. This paradigm may highlight the need for significant changes in how we approach the temporal dimension of treatment.

References

[1] Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. JAMA 2005. Published online October 20, 2005.

[2] Standiford TJ, Keshamouni VG, Reddy RC. Peroxisome proliferator-activated receptor-(gamma) as a regulator of lung inflammation and repair. Proc Am Thorac Soc 2005;2(3):226–31.

[3] Doux JD, Bazar KA, Lee PY, Yun AJ. Can chronic use of anti-inflammatory agents paradoxically promote chronic inflammation through compensatory host response. Med Hypotheses 2005;65(2):389–91.

Anthony J. Yun
Patrick Y. Lee
John D. Doux
Palo Alto Institute,
470 University Avenue, Palo Alto,
CA 94301, United States
Tel.: +1 650 387 6667; fax: +1 650 325 5028
(A.J. Yun)
E-mail address: ayun@stanford.edu (A.J. Yun)

doi:10.1016/j.mehy.2005.10.021

Avian flu virus H5N1: No proof for existence, pathogenicity, or pandemic potential; non-''H5N1'' causation omitted

WHO, CDC, Robert Koch Institute (RKI), and Friedrich Loeffler Institute (FLI) claim that H5N1 (avian flu virus) is ''highly contagious''. Further, Reinhard Kurth, president of RKI, says that

H5N1 ''threatens potentially all six billion people on earth''.

We identified four fundamental questions underlying these claims and requested supporting studies from FLI (which according to the German Government ''possesses virus isolates of H5N1''):

1. Does H5N1 exist?
2. Is it pathogenic to animals?
3. Is it transmissible and pathogenic to humans, and does it have pandemic potential?
4. Have other causes for observed disease been studied?

FLI responded with four papers: PNAS [1], Science [2], J Virol [3] directed towards questions 1 and 2; EID [4] towards question 3; PNAS [1] towards question 4.

Question 1 (existence). FLI responded with, ''H5N1/asia virus can be produced completely in vitro by using reverse genetics. The virus generated this way, also called infectious clone, cannot contain contaminants from sick animals'' [translated from German]. However, PCR cannot be used to identify viruses which have not been previously sequenced [5].

The PNAS paper (as the others) does not show or reference the composition of the stock virus — nor does Subbarao et al. (referenced by the EID paper), which claims first characterization of H5N1 disease in a human in 1997 [6]. Though the EID study failed to detect ''H5N1'' in several of the diseased organs, this anomaly was labelled an ''enigma'', rather than a ''contradiction''.

Robert Webster, corresponding author of the PNAS paper and Director of WHO's Collaborating Center for Studies on the Ecology of Influenza in Animals and Birds, informed us that stock viruses ''are classified as select agents'' and ''we are not at liberty to release this information''. Without verification, and without purification described in any of these papers, we cannot accept that stock virus is pure and fully characterized. Inquiries for clarification to Webster, CDC Select Agents Program, and FLI received no response.

Question 2 (animal pathogenicity). Papers describe the use of natural routes, but disease was only achieved with extraordinary concentrations, up to 10 million EID per animal. None of the experiments used controls or blinding. The Science paper is highly abstract molecular science, employing elevated concentrations of chimeric variants.

Question 3 (human pathogenicity and pandemic potential). The EID paper is an anecdotal report of a 6-year-old boy from Thailand with severe multi-organ disease. No evidence was given for transmissibility to humans. The scientists found evidence of aspergillosis, and the boy was treated with toxic agents (broad-spectrum antimicrobial and antivirals) before he died.

Subbarao et al. (referenced by the EID paper), describes a previously healthy 3-year-old Hong Kong boy who developed flu-like symptoms in May 9, 1997, and was treated with broad-spectrum antibiotics and salicylic acid, though this is commonly contraindicated. He developed Reye's Syndrome and died eleven days later [7]. A search commenced for causation within a limited range of flu viruses. H5N1 was claimed causative, even though coronaviruses, flaviviruses, enteroviruses, other pathogens and chemicals can also cause flu symptoms. There was no confirmation of prior avian contact. Regardless, warnings of an ''explosive pandemic'' appeared in this early document, though FLI conceded: ''There is no scientific forecasting method that can evaluate the possibility that an influenza virus induces a new pandemic.''

Question 4 (non-''H5N1'' causation). Neither the Subbarao et al study nor the FLI references consider reasonable, competing theories for disease causation, e.g., environmental and pharmaceutical factors.

Our analysis shows the papers do not satisfy our four basic questions. Claims of H5N1 pathogenicity and pandemic potential need to be challenged further.

References

[1] Hulse-Post DJ, Sturm-Ramirez KM, Humberd J, Seiler P, Govorkova EA, Krauss S, et al. Role of domestic ducks in the propagation and biological evolution of highly pathogenic H5N1 influenza viruses in Asia. Proc Natl Acad Sci USA 2005;102(30):10682—7.

[2] Hatta M, Gao P, Halfmann P, Kawaoka Y. Molecular basis for high virulence of Hong Kong H5N1 influenza A viruses. Science 2001;293(5536):1840—2.

[3] Hulse DJ, Webster RG, Russell RJ, Perez DR. Molecular determinants within the surface proteins involved in the pathogenicity of H5N1 influenza viruses in chickens. J Virol 2004;78(18):9954—64.

[4] Uiprasertkul M, Puthavathana P, Sangsiriwut K, Pooruk K, Srisook K, Peiris M, et al. Influenza A H5N1 replication sites in humans. Emerg Infect Dis 2005;11(7): 1036—41.

[5] Brown TA. The polymerase chain reaction. In: Genomes. 2nd ed. Bios Scientific Publishers; 2002 [chapter 4.3].

[6] Subbarao K, Klimov A, Katz J, Regnery H, Lim W, Hall H, et al. Characterization of an avian influenza A (H5N1) virus isolated from a child with a fatal respiratory illness. Science 1998;279(5349):393. p. 393—6.
[7] Hurwitz ES, Barrett MJ, Bregman D, Gunn WJ, Pinsky P, Schonberger LB, et al. Public Health Service study of Reye's syndrome and medications. Report of the main study. JAMA 1987;257(14):1905—11.

doi:10.1016/j.mehy.2005.11.007

David Crowe
Torsten Engelbrecht
Freelancer, Hein-Hoyer-Strasse 60, 20359 Hamburg, Germany
Tel.: +49 40 42103378 (T. Engelbrecht)
E-mail address: tengelbrecht@gmx.net (T. Engelbrecht)

Neoadjuvant chemotherapy with weekly paclitaxel in breast cancer patients may increase release of cancer cells into circulation by decreasing interstitial fluid pressure

To the Editor,

Paclitaxel is an effective agent in the treatment of breast cancer. Green et al. [1] reported the results of a randomized trial of preoperative chemotherapy comparing 12 weekly doses of paclitaxel (80 mg/m^2) followed by four cycles of 5-fluorouracl-doxorubicin-cyclophosphamide (FAC) with four 3-weekly doses of paclitaxel (225 mg/m^2) also followed by four cycles of FAC in 258 patients with operable breast cancer. Pathological complete response rates were 29% and 13% for those treated with weekly and 3-weekly paclitaxel, respectively ($P = .01$). Moreover, superiority of weekly compared with every 3-weekly paclitaxel in terms of response rate and time to progression was also shown in metastatic breast cancer [2]. One potential mechanism of weekly paclitaxel antitumor activity is that more frequent delivery of moderate doses may achieve greater efficacy than standard 3-weekly paclitaxel. More frequent exposure to paclitaxel may enhance its apoptotic and antiangiogenic effects [3]. Taghian et al. [4] in their study evaluated the interstitial fluid pressure (IFP) and oxygenation before and after neoadjuvant chemotherapy using sequential paclitaxel and doxorubicin in patients with breast cancer tumors of $\geqslant 3$ cm. In their phase II protocol, paclitaxel was administered on a weekly schedule at a dose of 80 mg/m^2 for nine cycles. They found that paclitaxel significantly decreased the IFP and increased the oxygenation, whereas doxorubicin did not cause any significant changes. Recent study by Pachmann et al. [5] showed that neoadjuvant chemotherapy with paclitaxel in breast cancer patients causes release of breast cancer cells into circulation, while at the same time reducing tumor size. During the applied combination therapy, three different phases were observed. A first decline in the number of circulating tumor cells during epirubicin containing part of regimen, followed by a steep increase during paclitaxel treatment and a subsequent re-decrease if a third regimen with cyclophosphamide—methotheraxe—5-fluoruracil combination was administered. We assume that since IFP may be a barrier for tumor cells entering into circulation, weekly paclitaxel may eliminate this barrier by decreasing IFP. Additionally, since circulating tumor cells correlate with patient outcome [6] and weekly paclitaxel may increase anthracycline drug concentration at tumor tissue level by decreasing IFP, giving weekly paclitaxel first then anthracycline in a sequential manner at neoadjuvant setting may be more optimal schedule in breast cancer patients.

References

[1] Green MC, Buzdar AU, Smith T, et al. Weekly paclitaxel followed by FAC as primary systemic chemotherapy of operable breast cancer improves pathologic complete remission rates when compared to every 3-week paclitaxel therapy followed by FAC — final results of a prospective phase III randomized trial. Proc Am Soc Clin Oncol 2002;20:33a [Abstract 135].
[2] Seidman AD, Berry D, Cirrincione C, et al. CALGB 9840: phase III study of weekly Paclitaxel via 1-h infusion versus standard 3 h infusion every third week in the treatment of metastatic breast cancer (MBC), with Trastuzumab (T) for HER2 positive MBC and randomized for T in HER2