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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 para-

digm may highlight the need for significant changes in how we approach the temporal dimension of treatment.

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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.

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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/m²) followed by four cycles of 5-fluorouracil-doxorubicin-cyclophosphamide (FAC) with four 3-weekly doses of paclitaxel (225 mg/m²) 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 ≥ 3 cm. In their phase II protocol, paclitaxel was administered on a weekly schedule at a dose of 80 mg/m² 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–methotrexate–5-fluorouracil 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.

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