Cardiovascular adverse reactions from NSAIDs are more than COX-2 inhibition alone

‘The gun must be loaded for COX-2 inhibitors to pull the trigger and cause cardiovascular toxicity’*

This editorial refers to ‘Association of myocardial infarctions with COX-2 inhibition may be related to immunomodulation towards a Th1 response resulting in atheromatous plaque instability: an evidence-based interpretation’, by Ireneusz T. Padol et al., doi:10.1093/rheumatology/kep225, on page 837.

Padol and Hunt hypothesize [1] that plaque instability and myocardial infarction (MI) contribute to cardiovascular (CV) reactions from NSAIDs, which arise from augmentation of lymphocyte Th1-type activation. The widely accepted dogma is that CV reactions from traditional NSAIDs and coxibs are caused by an imbalance of cyclo-oxygenase (COX)-2 inhibition by these drugs leading to reduced production of vasodilatatory prostacyclin (PGI2) from endothelia, whereas pro-aggregatory platelet thromboxane-A2 production is spared [2]. Although these effects may be important for the elevation of blood pressure and renal effects of NSAIDs [2], it is likely that the immuno-inflammatory reactions from reduced prostaglandin (PG) E2 occur within atheromatous plaque and associated blood vessel wall inflammation and so contribute to MI. This evidence-based suggestion has considerable importance for understanding the actions of traditional NSAIDs and coxibs.

Support for the Padol–Hunt hypothesis comes from their recent studies in mice with pronounced Th1 (C57BL/6) and Th2 (Balb/c) lymphocyte responses. The mice were given sub-ulcerogenic doses of diclofenac for 7 days in which the serum levels of a range of cytokines were increased, reflecting an exaggerated Th1 level to the drug treatment [4]. These results suggest that the drug treatment improved Th1 cytokines (e.g. IL-2 and -17), although there was an increase in both strains of IL-6, CRP and the leucocyte chemokine, MCP-1. The results further support the role of a traditional NSAID in mediating exaggerated Th1 response. Further investigations in mouse strains with other NSAIDs (including coxibs) alone and in the above inbred strains of mice in which collagen II arthritis is induced would provide insight into the potential mechanisms of the Th1 response in a chronic inflammatory disease, which is a well-accepted animal model for human rheumatic disease.

Further evidence for the role for COX-2 inhibition altering Th1/2 lymphocyte responses has been shown in recent studies by Hamada et al. [5] in liver ischaemia reperfusion injury in COX-2 deficient mice. The hepatic injury, neutrophil accumulation and apoptosis were reduced in COX-2 deficiency compared with wild-type animals along with decreased IL-2 and -12, a Th1 cell differentiation cytokine. Again, COX-2 activity was reported to be important in the Th1 exaggerated response, thus supporting Padol and Hunt’s recent results in mice [4].

Many patient-related factors could, however, contribute to NSAID-associated CV pathology, which include variability in CV events with different NSAIDs [6, 7] and the increased risk of CV disease with RA independent of the involvement of drugs [8]. Most data calculations of risk show high values of confidence intervals [6, 7]. Few investigations have considered the possibility that there may be a variety of risk factors underlying the occurrence of CV events, which begs the need to examine what factors underlie the association of CV reactions with intake of coxibs and traditional NSAIDs.

Among these factors is the role of rheumatoid disease and high rates of infections. Thus, atherosclerosis like RA is a Th1-driven disease [9]. Microbial infections among these Helicobacter pylori and Porphyromonas gingivalis (in periodontal disease), are both associated with CV diseases in RA [10–19]. Helicobacter pylori has been found in atheroma plaque [12, 13] and aorta [14], and causes endothelial dysfunction [15], pro-aggregatory effects on platelets [16] as well as elevated levels of TNF-α and eliciting a Th1 response [12]. RA patients with periodontal disease have elevated levels of TNF-α [18] and exaggerated antibody response to P. gingivalis [19] above those without periodontitis.

Initially, concerns about CV risks arose from patients with RA who received rofecoxib alone [5, 6, 20] [e.g. the Vioxx Gastrointestinal Outcomes Research (VIGOR) study] who were not permitted cardio-protective aspirin [20]. Half the patients in the VIGOR study received glucocorticoids [20], a risk factor for CV disease in arthritic patients [7]. Other studies with celecoxib were predominantly in OA with fewer RA patients who were allowed cardioprotective aspirin [21], thus reducing CV events [6].

The Therapeutic Arthritis and Gastrointestinal Event Trial (TARGET) study comparing lumiracoxib with naproxen and ibuprofen was done in patients with OA, but 44–47% of these patients with gastrointestinal adverse reactions had H. pylori infection [22].
Presumably, these patients were infected with this organism in the CV study [23].

To understand if the risk of CV from NSAIDs is higher in RA than in OA, pharmaceutical companies with data from large-scale trials with coxibs might consider pooling their data so that an analysis of CV risks can be established with NSAIDs in patients with RA vs OA.

Besides preventing atherosclerosis, statins control chronic inflammatory reactions in RA [24, 25] and have been promoted for treating it [26–28]. They may act in these conditions by preventing Th1-mediated immuno-inflammatory reactions that underlie both atherosclerosis and RA [23, 24]. Optimizing anti-inflammatory therapy with combinations of low-dose NSAIDs and statins might reduce risks of serious gastrointestinal, hepato-renal and also CV adverse reactions from lower doses of NSAIDs.

Thus, the Padol–Hunt hypothesis gives us considerable insight into the role of T-cell subsets in the aetiology of NSAID-associated CV as a consequence of the effects of inhibiting COX-2-derived PGE2. The disease manifestations of RA and co-infections with H. pylori and P. gingivalis all seem to exacerbate or contribute to CV, especially unstable plaque and MI by increased production of pro-inflammatory cytokines in these states and Th1-mediated atherogenesis. The Padol-Hunt hypothesis poses important questions regarding the nature of drug-disease interactions, which deserve further investigation in experimental animal models of CV disease.

A possible consequence of the involvement of Th1-driven immuno-inflammatory reactions in both RA and CV reactions to NSAIDs is the potential for statins to control Th1-immuno-inflammation in both these states. Therapeutic trials should be undertaken in RA to (i) optimize the doses and combinations of statins with low doses of selected NSAIDs (e.g. celecoxib, etoricoxib, diclofenac, ibuprofen, naproxen); (ii) to measure the pharmacologically important mediators of Th1 (and possibly Th17) cytokines, CRP and other disease biomarkers in relation to therapeutic responses to these drug combinations; and (iii) investigate the roles of H. pylori and P. gingivalis in the Th1 responses in these diseases.

Disclosure statement: The author has declared no conflicts of interest in relation to this topic, but has been a consultant to several companies marketing NSAIDs: IBSA (Hull, UK), Panacea (New Delhi, India) and Reckitt Benckiser (Hull, UK).

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