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

Ireneusz T. Padol1 and Richard H. Hunt1

See page 834 for the editorial comment on this article (doi:10.1093/rheumatology/kep451)

Abstract

Cyclooxygenase (COX) inhibitors remain a major class of drugs in rheumatology and their widespread use is expected to continue. The view that a prothrombotic effect explains the increase in myocardial infarction (MI) associated with both COX-2 selective and traditional NSAIDs (tNSAIDs) has been increasingly questioned. We review the evidence that prostanoids direct the immune response away from a Th1 response and that consequently inhibition of prostaglandin synthesis results in augmentation of the Th1 response by limiting prostanoid synthesis. Although the role of prostanoids as mediators of inflammation in the periphery is well understood, the systemic immunomodulatory role of prostanoids shifting the immune response away from a Th1 type is less appreciated. Atherosclerosis is an inflammatory arterial disease driven by a Th1 type immune response. Moreover, the vulnerable phenotype of atheroma is associated with the cellular Th1 immune response in contrast to the stable plaque phenotype associated with a Th2 type response. We propose a class effect of COX-2 selective and tNSAIDs, which results in augmentation of Th1-mediated atherogenesis/production of pro-atherogenic cytokines associated with detrimental plaque remodeling, instability, rupture and embolization resulting in MI. Understanding of the Th1 mediated immunity, which underlies the cardiovascular, and the non-Th1, which underlies gastrointestinal adverse effects associated with the use of COX inhibitors, should lead to better risk assessment and the development of anti-inflammatory treatments with improved safety. Our explanation also emphasizes the pharmacological effects and consequences of immunomodulation in the inflammation associated with atherosclerosis and other Th1- as well as non-Th1-driven diseases.

Key words: NSAIDs, Anti-inflammatory drugs, Cardiovascular risk, Gastrointestinal risk, Anti-rheumatic agents, Prostaglandins, Immunomodulation, Atherosclerosis, Atheroma, Myocardial infarction.

Introduction

In the USA, NSAIDs are taken once per week by 70% of those aged >65 years and half of them take at least a daily dose [1]. NSAIDs are widely used medications for RA, OA and other rheumatic diseases, and their use is expected to continue with the aging of the population. The development of selective cyclooxygenase-2 (COX-2) inhibitors (COXIBs) was driven by the challenge of lessening gastrointestinal adverse events seen with widespread and increasing use of traditional NSAIDs (tNSAIDs). However, use of COXIBs revealed an increase in the incidence of myocardial infarction (MI), subsequently found to be a class effect of NSAIDs. Until now, no prevailing hypothesis exists to explain these effects. Most, if not all, recent attention has focused on the prothrombotic properties of selective COXIBs. The initial and widely accepted explanation for this finding was an imbalance between
COX-derived prostanoids, with the target COX-2 being effectively inhibited, resulting in prostacycline depletion, whereas COX-1-mediated thromboxane activity was spared. This imbalance was postulated to increase prothrombotic risk (thromboxane A2) while inhibiting the effect of prostacycline (PGI₂) protection from thrombosis [2]. The beneficial role of PGI₂ on cardiovascular (CV) system is well established, but the role of PGE₂ is more complex. The role of prostanoids and CV system has been recently reviewed [3]. The subsequent evidence is that most of the tNSAIDs also increase the risk of MI to a similar extent as COXIBs has provoked questioning of this hypothesis [4–11]. In particular, there is no evidence for an increase in peripheral vascular thrombosis, deep venous thrombosis (with or without pulmonary embolism), renal, portal or hepatic vein thrombosis; and only one study has suggested an increase in thrombotic stroke [12]. Other explanations and contributing factors for adverse cardiovascular effects with COXIBs include elevated blood pressure, abnormal vascular remodelling, inhibition of protective mechanisms against ischaemia–reperfusion injury and inhibition of 15-epi-lipoxin production [13]. Thus, our arguments provide an alternative mechanism to the outlined scenarios. In particular, our interest in this area was triggered by the question whether patients at high risk of gastrointestinal adverse events are the same as those who are at high cardiovascular risk. A critical evaluation of the literature has led us to the concept that cardiovascular and gastrointestinal risks associated with COX inhibition are in general mutually exclusive and that they align with the Th1 and Th2 dichotomy, and consequently to immunomodulation of atherosclerosis (Fig. 1A and B). In this review, we provide an evidence-based alternative explanation to the so-called prothrombotic effect of COX-2 selective and tNSAIDs.

We propose that the primary event leading to MI is not thrombosis but rather the nature of the arterial inflammation and vulnerability of plaque for rupture. Furthermore, since MI in patients on anti-inflammatory drugs has been observed predominantly in patients with arthritis, it is not clear whether the propensity for MI is related to the anti-inflammatory drugs or to their underlying genetic or acquired/environmental predisposition to inflammatory diseases or a combination of both. Thus, the continued necessity for medications that inhibit COX has emphasized the need for a workable hypothesis and particularly development of potential markers, which would help to identify patients at cardiovascular or gastrointestinal risk, or both. We propose a new explanation of COX-2 inhibition and the increased risk of MI: this explanation involves the interactions of COX-derived prostaglandins (PGs) with the immune system and the Th1 and non-Th1 type responses in particular, and also explains their reciprocal dynamics on plaque instability and its consequences.

Evidence

There are principally two polarized forms of cytokine profile: Th1, which leads to a complex cellular immune response involving T cells and macrophages, and Th2 or non-Th1 profile, leading to a humoral immune response with typical involvement of B cells and production of antibodies. The uncontrolled and persistent Th2 type immune response may be associated with atopic diseases such as allergies or allergic asthma. Conversely, an uncontrolled and persistent Th1 type immune response is at the core of many diseases in which inflammation leads to

Fig. 1 (A) In the gastric mucosa PGs modulate acid secretion, blood flow and mucosal defense. In the absence of COXIBs, there are no known gastropathies related to the varying physiological levels of PG. However, systemically, levels of PG synthesis determine a homoeostatic gradient between Th1 and Th2 responses with overall effect of shifting the immune response towards Th2. (B) Acute inhibition of gastric PGs by tNSAIDs leads to rapid onset of gastropathy, which is greater in those with a Th2 response. Chronic inhibition of PG synthesis by COX-2 selective and tNSAIDs leads to immunomodulation of the immune response towards Th1, which in turn contributes to atheromatous plaque instability and consequently MI in predisposed (Th1 predominant) individuals.
pathological changes and clinical symptoms. In particular, a Th1 response is characteristic of chronic inflammatory diseases such as RA, Crohn’s disease and most importantly, atherosclerosis [14–16]. The potential involvement of the Th17 response will be discussed later.

Atheromatous plaques form as a consequence of atherosclerosis, and the stability of the plaque (unstable or stable) is determined by its composition and morphology. An unstable plaque is associated with a Th1 immune response, and is mainly composed of inflammatory cells, particularly T cells, neutrophils and macrophages, which contain lipids, predominantly low density lipoprotein (LDL), leading to the formation of foam cells [17, 18]. By contrast, a stable plaque is associated with a Th2 response and predominantly composed of smooth muscle cells, collagen secreting cells and collagen [18, 19]. Shifting from the former Th1-driven to the latter Th2-driven inflammation results in attenuation of atherosclerosis and remodelling of atheromatous plaque away from the unstable inflammatory cell based towards the more organized and stable smooth muscle- and collagen-composed plaques [20–23]. This shift towards a Th2, or away from a polarized Th1 response, subsequently results in a lower risk of plaque rupture and the consequences of stroke and MI [24–26] otherwise prevalent in Th1 individuals [27, 28]. Immunomodulation towards Th2 is considered as a viable therapeutic approach to combat atherosclerosis [29], and some authors have suggested that a Th2-driven helminth infection might attenuate cardiovascular disease(s) and the associated risks and consequences [30].

Th1 and Th2 immune responses rely on the production of type-specific inflammatory cytokines, such as IFN-γ, IL-12, -2 (Th1) or -4, -10, -13 (Th2). These and other inflammatory mediators determine selective, in general mutually exclusive and antagonistic, Th1 or Th2 responses that influence and amplify the course of the inflammation-driven disease, such as atherosclerosis. Any immunomodulation by drugs such as statins, or as proposed here, COX-2 selective and tNSAIDs may affect this balance and influence the course of atherosclerosis. The type of immune response evoked does not necessarily reflect the type of infectious agent causing inflammation. In general, viral, bacterial, fungal and protozoan organisms evoke a Th1 response, whereas allergens and parasites evoke a Th2 type. However, the type of response is also host/patient dependent and determined by genetics as well as exposure to environmental factors. For example, the controlled hygienic environment, which eliminates parasitic infections and, as we argue, COXIBs or other immunomodulatory agents as well as genetic selection may shift predominance of the immune response towards the polarized Th1 type. The consequences are reflected in the high incidence of Th1-driven chronic inflammatory diseases in developed countries [31].

There are many ways to modulate the immune response to reduce a Th1 and promote a Th2 response to ameliorate atherosclerosis. They include immunization with parasitic antigens, use of Th2 cytokines such as IL-10 or its gene transfer, use of IFN-γ inhibitory protein, chemokine inhibition or blockade, use of an anti-CD40 ligand, mycobacterium, adjuvants and of course the use of statins [32–38]. Here, we focus on the immunomodulatory role of prostanoids.

PGs are ubiquitous molecules produced by every human cell. Besides their typical, organ-dependent (e.g. gastroprotective and renovascular) physiological functions, COX-derived PGs skew the immune response away from Th1 towards Th2, thus, establishing a link between prostanoid metabolism and the immune system [39–47]. However, the clinical evidence is scarce and warrants clinical and epidemiological studies exploring the therapeutic effects of PGs/COXIBs on immunomodulation. Inflammation induces COX-2 leading primarily to the production of a variety of eicosanoids, and it is predominately expressed over COX-1 in atherosclerotic plaque [48]. COX-2-derived PGE2 inhibits Th1-driven cellular responses and is essential for Th2 responses [49–51]. This effect is complemented by the fact that two key Th2 cytokines, IL-4 and -10, inhibit PGE2 production and thus provide negative feedback, which likely contributes to the control of the inflammatory cascade [52, 53]. Moreover, PGE2 inhibits human NK activity but promotes B lymphocyte Ig isotype switching to IgE [54, 55]. Consequently, inhibition of COX-2 by selective and tNSAIDs results in augmentation of the Th1 and impairment of the Th2 response, and thus leading to enhancement of pro-inflammatory cellular responses with simultaneous suppression of the humoral response [56–66]. Therefore, we suggest that COX-2 selective or tNSAIDs induce a Th1 response resulting in T cell and macrophage accumulation at the site of inflamed arterial endothelium. This response leads to the production of pro-atherogenic cytokines, which further attract lymphocytes and macrophages leading to exacerbation of inflammation, increasing plaque instability and vulnerability to rupture, embolization and consequent MI. Conversely, non-Th1-driven inflammation allows for a Th2 dominant pathway in atherosclerosis with plaque containing less reactive immune cells, more collagen and collagen producing cells, smooth muscle cells and cells secreting antibodies against oxidized LDL. Thus, the type of immune response has a profound effect on plaque stability with Th1-driven responses and inflammation being seriously detrimental and Th2 responses offering the possibility of some protection from the consequences of atherosclerosis [17, 19, 20, 22–25, 27].

In our evidence-based analysis, the relatively new concept of the Th17 immune response aligns with the Th2 response. Systemic PGE2 increases the Th17 response, and vice versa, and IL-17 up-regulates COX-2 expression and increases PG production [67, 68]. In addition, PGE2 induces a shift in the IL-23/IL-12 balance in favour of IL-23, resulting in increased IL-17 production, presumably through the amplification of self-reactive Th17 cells [69, 70]. As these findings of the involvement of the Th17 response, through a pro-inflammatory role of
PGE₂, have been implicated in autoimmune diseases such as RA, the immunomodulatory role of COXIBs reversing this pressure might be of importance.

There is also an additional scenario associated with COX inhibition. Reduced vessel wall inflammation is likely to result in an improvement in arterial wall compliance but with the potential for destabilization of plaque and increased risk of fragmentation, detachment and embolization. Furthermore, an increase in the incidence of MI may not necessarily lead to increased mortality, as the fatal infarctions in the placebo-controlled Adenomatous Polyp Prevention on Vioxx (APPROVe) study were approximately the same in the COXIB and control groups (two and three, respectively), with the total numbers of all MIs more than double, with 21 in the COXIB vs nine in the placebo group. This is in line with data from an animal model, which showed that the size of a standardized experimental infarct was reduced in a COXIB pre-treated compared with placebo group [71].

None of these scenarios involve an increase in thrombosis per se. Rather, they suggest interpretation of the observed drug effects based on the nature of the inflammation of the arterial wall stemming from the Th1 type immune response, which may be patient dependent. Our concept distinguishes the beneficial role of PG inhibition at the localized site of inflamed tissue but emphasizes that COX inhibition is systemic and neither site nor organ specific. Thus, immunocytes throughout the body will be simultaneously and indiscriminately subjected to immunomodulation by the reduced levels of PGs that occur. The time to MI in patients on COXIBs is in keeping with the concept that ‘detrimental’ immunomodulation is a slow process, since nearly all MIs occurred in clinical trials of >12 weeks [9]. This is in contrast to the expected shorter time to MI if thrombosis was at the core of COX inhibition-associated MI.

Support for our interpretation also comes from several animal models. It is well-known that C57BL/6 mice have a polarized Th1 response, whereas Balb/c mice are characterized by a Th2 immune response. Thus, not surprisingly Balb/c mice are resistant to the induction of atherosclerosis, whereas C57BL/6 mice are highly susceptible, leading to the use of this strain as a model for atherosclerosis [72, 73]. Moreover, we have shown that Th2 predominant Balb/c mice are more susceptible to NSAID-induced gastropathy than Th1-predominant C57BL/6 mice and that the PG physiology is also strain specific [74]. Acid secretion is not inhibited by PGs in the C57BL/6 mice because of their 5-fold lower expression of EP₃ receptors on gastric parietal cells as compared with Balb/c mice. Thus, in C57BL/6 mice acid secretion is unchanged, despite inhibition of PGE₂ by NSAIDs, resulting in less mucosal damage in contrast to Balb/c mice. C57BL/6 mice also lack secretory group II phospholipase A₂, an enzyme essential for the production of PGs, thus reducing or impairing PG synthesis [75]. This process directs the immune response away from a Th2 type and may be pivotal in explaining why these mice respond to infections in a Th1 fashion.

These observations are consistent with our new concept of a mutually exclusive risk for gastrointestinal and cardiovascular adverse events associated with COX inhibition. However, the underlying mechanisms differ as gastric damage is acute in nature relying on inhibition of the physiological properties of PGs, whereas the latter is a slow process depending on the immunomodulatory effects and remodelling of atherosclerotic plaque (Fig. 1B). The analogy for our concept of atherosclerosis being adversely immunomodulated by COXIBs is the converse of the additional effect of statins that derive a substantial portion of their therapeutic activity from a beneficial immunomodulation of this inflammatory disease [34, 76–78].

Relevance

It is well-known that patients with active Th1-driven disease such as RA have a higher incidence of MI than patients with OA, which is less dependent on active inflammation [79, 80]. We believe that patients who fit an inflammatory profile, driven predominantly by the Th1 type immune response, may be affected differently by COX inhibition than those who have a non-Th1 type inflammatory profile. Thus, we suggest that the drug class effect of COX-2 selective and tNSAIDs results in a shift towards a polarized Th1 immune response, remodelling atheromatous plaque towards the unstable plaque morphology, which is associated with adverse cardiovascular consequences including MI. In addition, our proposed hypothesis may suggest or provide a mechanistic explanation for the immunomodulatory effect of COX inhibition being detrimental to other Th1-driven diseases such as Crohn’s disease [81, 82]. There is neither a comprehensive hypothesis-driven report that MI prevalence is increased in Crohn’s disease, nor that atopic diseases are inversely associated with MI. However, clinical experience and numerous reports suggest that COXIBs exacerbate inflammatory changes in Crohn’s disease. These observations warrant prospective investigation.

Clinical studies should examine the immunomodulatory role of anti-inflammatory agents. If our hypothesis is correct, it should be feasible to identify patients or populations with a predominance of the Th1 type immune profile as compared with those with a more balanced Th1/Th2 or typical Th2 profile and assess the MI rates. Retrospective studies could examine the existing data for differences in MI rates between Th1 patients such as those with RA or cardiovascular disease and non-Th1 patients such as OA patients or normal healthy subjects from clinical trials of tNSAIDs or selective COXIBs. Such studies are important, because they would enable identification of individuals at greater risk of cardiovascular or gastrointestinal adverse events while on anti-inflammatory treatment involving COX inhibition. Furthermore, research in this area would help design optimal pharmacological strategies for the safer use of anti-inflammatory drugs regardless of the patient-dependent type of immune response and take into the consideration their immunomodulatory properties.
Conclusion

We offer a novel explanation for the pharmacological modulation of the immune system through inhibition of COX pathway. We propose a plausible rationale for the increased incidence of serious adverse cardiovascular events, including MI, associated with COX inhibition and which stems from atheromatous plaque instability by augmentation of the Th1 type immune response or production of pro-atherogenic cytokines with the use of drugs, which inhibit COX, or both. This rationale provides an opportunity for viable approaches to improved cardiovascular and gastrointestinal risk assessment, with the use of currently available anti-inflammatory agents in rheumatology and their impact on diseases driven by Th1 as well a non-Th1 immune response. Moreover, we emphasize the importance of prostanoid metabolism in the immunomodulation of inflammatory diseases. Although we have drawn attention to the cardiovascular and gastrointestinal consequences of this immunomodulation, our hypothesis offers a better understanding and the prospects of novel, more comprehensive therapeutic approaches in other inflammatory diseases. Moreover, it provides a direction for basic and clinical research related not only to COX inhibition, but also to other drugs possessing immunomodulatory properties.

Rheumatology key message

- NSAID-induced immunomodulation may promote production of pro-atherogenic cytokines leading to plaque instability and MI.

Acknowledgement

I.T.P. and R.H.H. are sole authors who initiated and generated this evidence-based review and wrote the manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

References


et al
66 Goodwin JS, Bankhurst AD, Murphy SA, Selinger DS, Tsuboi I, Tanaka H, Nakao M, Shichijo S, Itoh K.
65 Andreone P, Gramenzi A, Loggi E et al
61 Muthian G, Raikwar HP, Johnson C
60 Turull A, Queralt J. Selective cyclooxygenase-2 (COX-2) inhibition promotes B lymphocyte Ig isotype switching to IgE. J Immunol 1995;154:162–70.
74 Padol IT, Hunt RH. Host-specific differences in the physiology of acid secretion related to prostaglandins may play a role in gastric inflammation and injury. Am J Physiol Gastrointest Liver Physiol 2005;288:G1110–17.