The patient was then successfully treated with colchicine (0.5 mg/day) and low-dose steroids both given for her purpura and arthritis, while peripheral neuropathy was treated with gabapentin. Shortly after, steroids were tapered and then suspended.

HCV-related MC syndrome is an immune-complex type of vasculitis characterized by the usual association of HCV infection with the cryoglobulin production by non-neoplastic RF-positive proliferating B-cell clones. Therefore, MC syndrome represents an autoimmune disorder where the etiology can be known and the trigger antigen can be potentially targeted. However, pathogenic events, involving the immune system downstream the triggering infection, may become independent from the initial stimulus, as supposed in other autoimmune diseases [10]. Our case of MC syndrome developed after HCV eradication highlights this hypothesis. Previously, Beuthien et al. [5] reported a case of cryoglobulinaemic vasculitis diagnosed ten months after the beginning of pegylated-IFN treatment for HCV. Notably, in this report HCV-RNA was undetectable at the time of MC syndrome diagnosis, though the patient was still undergoing IFN therapy. In contrast, MC syndrome was diagnosed 4 yrs after the end of the antiviral treatment in our patient. Therefore, based on time to onset, MC vasculitis might be thought as an IFN-related complication in the aforementioned case [5], while it is unlikely in our patient, where vasculitis appeared independently from IFN therapy and in the lack of active HCV replication. It can be argued that HCV or IFN or both had altered the immune system homeostasis and predisposed to autoimmune phenomena. Subsequent events (e.g. asymptomatic or paucisymptomatic infection, BLyS upregulation, other environmental factors) may have been crucial to spark off the autoimmune disease on a genetic predisposing background [6, 10]. In this regard, therapeutic strategies which target either the viral trigger HCV, if present, and/or the proliferating B-cells directly or indirectly may be equally useful and should be equally explored by larger studies in the next future.

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“To do no harm”

Sir, We read with interest the article by Walker and Moots [1]. We share their apparent frustration with the recent withdrawal of rofecoxib, valdecoxib and co-proxamol. However, we feel in order to reach a balanced view on this argument, we need to explore the logics and reasoning behind the decision to withdraw these drugs.

The first question we should ask ourselves surely is, would any pharmaceutical company of world renown, simply withdraw a universally acclaimed product and relinquish a market worth billions without clear and compelling reasons for doing so? We agree that the industry feared an unacceptably high level of future litigations, which forced immediate drug withdrawal. This fear was based on an in-depth knowledge of the anticipated size of the cardiovascular and cerebrovascular side effect profile related to COX-2 inhibitors if their use was allowed beyond that time. Furthermore, following the voluntary withdrawal of rofecoxib by Merck Sharp & Dohme (MSD), the Food and Drug Administration (FDA) reviewed the available evidence and asked Pfizer to withdraw valdecoxib and revise labelling for all non-steroidal anti-inflammatory drugs (NSAIDs) to highlight the potential increased risk of cardiovascular events [2].

Dr Walker and Moots downplayed the size of the risk attached to the use of these drugs. We doubt very much that the decision to withdraw the three drugs was made hastily nor was it a commercial decision by the drug industry. The decision to withdraw was based on high quality data [3, 4, 5] and a prolonged monitoring campaign. We always believe that prospective, randomized, controlled clinical trials are the best way to evaluate the safety of medicines. The voluntary withdrawal of rofecoxib (Vioxx) by MSD in September 2004 was based on 3-yr data from a
prospective, randomized, placebo-controlled clinical trial, the APPROVe (Adenomatous Polypl Prevention on VIOXX) trial [6]. In this study, the risk of myocardial infarction is doubled in patients on rofecoxib compared with those taking placebo. Rofecoxib’s cardiovascular toxicity was highlighted soon after its launch in 2000 based on the VIGOR (VIOXX GI Outcomes Research) study [4]. The Arthritis Advisory Committee added ‘increased cardiovascular side effects’ to the labelling for rofecoxib in April 2002. Withdrawal then became inevitable in 2004, following the overwhelming data that eventually confirmed the long-suspected unacceptable increase in the morbidity and mortality associated with the use of rofecoxib.

It has been known for over 20 yrs that co-proxamol (combination of dextropropoxyphene and paracetamol) is unique amongst paracetamol-containing analgesics in that it can cause death within 1–2 h (coma, severe respiratory depression, convulsions and cardiac arrest may occur within 30 min [7]). Symptoms occur so rapidly, that the majority of deaths (~80%) with this agent occur before patients reach hospital. The Committee on Safety of medicines (CSM) first warned prescribers about the risks of co-proxamol in 1985, but despite being rated as ‘less suitable for prescribing’ by the British National Formulary (BNF) it is still widely used. There has been no reduction in toxicity and fatal overdose [8]. The national statistic report for 2006 estimates deaths related to co-proxamol poisoning for England and Wales between 2000–2004 at ~300 deaths per year [9], which is several times more than deaths due to ecstasy. Many of these deaths (~1/5) are due to accidental overdose. Co-proxamol overdose is associated with a 10-fold excess mortality compared with other paracetamol combination analgesics such as co-codamol and co-dydramol [10]. This was attributable to inherent toxicity and not to increased use in overdose. In view of the high toxicity of co-proxamol, especially when combined with alcohol, and the fact that the risk of overdose extends beyond the person the drug is prescribed for (particularly in young people), phased withdrawal from the market was considered the most appropriate option, especially if less dangerous alternatives are available. (The Medicines and Healthcare products Regulatory Agency (MHRA) issued CSM pain management guidance to help doctors find suitable alternatives for individual patients [11].

The authors attempted to exaggerate the void left in pain and inflammation treatment as a result of withdrawal of these drugs. They cited an anecdotal report ‘Many patients “swear by” the effect of one drug and not that of another’ and ignored a large volume of class one data [12, 13], which does not support a comparison of end organ toxicity.

In deciding what might be the most effective strategy for future drug withdrawal one needs to consider the variability in characteristics of those at risk, efficacy as well as the level of risk. Doubling the risk of myocardial infarction and stroke in order to control chronic dull ache and stiffness due to arthritis seems a logically unacceptable practice especially when alternative therapies—not proven as toxic as the drugs in question—are readily available.

We believe that in this instance the pharmaceutical industry and the regulatory bodies have fulfilled their contractual and moral duties towards patients and the public at large, putting patient interest and safety at the centre of their policies.

Following the COX-2 withdrawals, A Drug Watch Program and New Drug Safety Initiative was introduced by the regulatory bodies FDA and MHRA. Patients are taking a more active role in their healthcare provisions and play a major role in decision-making. Easier access to information on drugs licenced and deemed safe by the pharmaceutical industry will only benefit this process.

We strongly endorse the current regulatory measures that allow immediate drug withdrawal and recall. Though the shared model of medical decision-making has been proposed as the preferred method of determining patients’ treatment, agreement is often difficult to achieve if patients’ and clinicians’ preferences are polarized [16]. This is true when significant risk is well-established in terms of size and direction (end organ toxicity).

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To Do No Good

Mrs F.W., a 57-year-old nursing home manager, presented with a polyarthritis and plantar fasciitis in association with psoriasis in 2003. She was already taking meloxicam and co-proxamol. Her ESR was 51 and rheumatoid factor was 80. She was labelled as suffering from psoriatic arthritis. Because of indigestion she was changed to celecoxib, which was ineffective and then valdecoxib (even though it was not specifically licensed for psoriatic arthritis), which she found both tolerable and highly effective. She also continued on the co-proxamol, which she liked.

In January 2005, her GP was unwilling to prescribe co-proxamol following the CSM announcement that it was to be withdrawn. She assures us that she was not consulted by the CSM and therefore regards this as unilateral. She was then tried on co-codamol then tramadol and finally, simple paracetamol. None of these were as effective as the co-proxamol for her. She complained of more pain and was angry that she was refused the co-proxamol. She is told that there is no evidence from studies using aggregated data from large populations that co-proxamol is more effective than other analgesics. She replies that it certainly works better for her and that she was not included in any of the studies. ‘Does the only evidence that applies directly to me not count?’

Worse was to come in April, when valdecoxib was voluntarily (and unilaterally) suspended. She has since been changed to Sulindac, which is not as effective and which she cannot take continuously because of indigestion. ‘But I am not one of the two people in the UK who got Stevens Johnson from this and as I had been on it for 9 months I understand that my risk was even smaller’.

So, as we sit opposite Mrs F.W. (or any of hundreds of similar patients) in our clinic, we are thinking:

(1) I wonder how many doctors were in the MSD board-room when they decided to withdraw Vioxx? Perhaps there were a few accountants and lawyers who were making a commercial decision on behalf of their shareholders and they interpreted the scientific evidence in the context of the shareholders’ interest. Maybe they got it wrong!

(2) If the evidence is so precise, why have the FDA and the EMEA come to such different conclusions about the CV risks of coxibs and traditional NSAIDs?

(3) How could studies of the wrong dose of the drug in the wrong disease have caused so much trouble for this lady! Imagine the criticism if we were allowed to extrapolate wildly like that in treating patients in other circumstances!

(4) Is the Drug and Therapeutics Bulletin always right?

(5) Should not the benefit/risk ratio for drugs be considered on an individual basis, together with the patient, and in the light of relevant evidence, rather than the paternalistic (and scientifically grossly flawed) way that we are now being asked to adopt without question?

(6) If you just look at the published data without the context of real people who take drugs as they see fit, rather than as per protocol, then you can end up writing a daft editorial on management and conclude that ‘therapeutic touch’ is cost effective for OA [1].

(7) The current ranking of evidence does not take account of the size of the effect – so taping the patella or using a gel have better evidence than knee replacement!

We are most grateful to Binymin and Phillips [2] for engaging in the debate that we have wished to stimulate and providing us with the opportunity to publish this case report. Unfortunately their statement ‘Doubling the risk of myocardial infarction and stroke in order to control chronic dull ache and stiffness due to arthritis seems a logically unacceptable practice . . .’ is so far away from our patients’ experience that we do not feel we have enough common ground to even have an argument. Twice very little is still very little!

Potential conflict of interests. The authors treat many patients with pain from arthritis. The authors have sat on advisory boards for the drug industry.

Conflict of interest: None of us like sitting opposite patients in pain when there have been better drugs made for them.

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Comment on: Parotid gland biopsy compared with labial biopsy in the diagnosis of patients with primary Sjogren’s syndrome

Sir. We read with interest the report of Pijke et al. [1] comparing parotid gland with labial biopsy in 35 patients with Sjogren’s syndrome. The authors report a diagnostic sensitivity of 78% with these methods, and a 6% incidence of permanent sensory loss with labial biopsy. In contrast to these findings, we published our experience with an office-based method of labial gland biopsy in which over 100 biopsies were performed, diagnostic sensitivity was 100%, and long-term sensory loss was 0% [2]. Our current experience is with over 350 patients in which only one individual has suffered from permanent sensory loss.

We suggest that the decision as to which biopsy be performed be based on all available techniques, and not be limited to the question of which gland (labial vs parotid) to biopsy.

The authors have declared no conflicts of interest.