expressed in cultured FLS from OA patients as well. Increased RANKL expression in cultured FLS derived from RA patients has been reported previously [4, 5]. In the presence of TNF-α, RANKL expression from FLS was significantly decreased, as demonstrated by RT-PCR analysis and northern blot analysis (Fig. 2B and C). On the other hand, treatment of FLS from OA patients had no effect on the induction of RANKL.

RANKL is the main osteoclast-stimulating factor and OPG functions as a decoy receptor for RANKL, thereby acting as an inhibitor of RANKL-mediated bone resorption. It is therefore suggested that the balance between RANKL and OPG is important in the regulation of the bone microenvironment [6]. Without stimulation, FLS from our OA patients expressed a significantly increased level of OPG and a decreased level of RANKL compared with active RA patients. OPG expression in FLS from OA patients would be important in the protection of bone destruction. The expression of OPG and RANKL in FLS from OA patients was not significantly altered even in the presence of the potent inflammatory cytokine TNF-α. In contrast, RANKL, but not OPG, was abundantly expressed in FLS from our RA patients without stimulation. In addition, RANKL and OPG expression in FLS from RA patients was significantly modulated in the presence of TNF-α. RANKL-dominant expression, along with the lack of resistance against TNF-α of FLS from RA patients, may contribute to the pathogenesis of bone loss in RA.

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Reply

Harashima *et al.* produce some interesting results concerning OPG and RANKL mRNA production by RA and OA synovial fibroblasts. Unfortunately, there are several reasons why it is difficult to relate the results of Harashima *et al.* to the results presented in our recent paper [1].

No clinical details are provided on the RA or OA patients other than a statement that the RA patients are 'active'. It would be helpful to know about disease duration, previous and current treatment, joint scores and levels of inflammatory markers.

All the results from Harashima *et al.* relate to mRNA production, and no evidence is presented to show that this mRNA results in OPG and RANKL protein production.

In addition, all the results relate to type II synovial fibroblasts grown in tissue culture; there are no results relating to other relevant inflammatory cell synovial infiltrates. Our immunohistochemical labelling results show that the major sources of OPG protein are type I synovial macrophages and endothelial cells [1], while the major source of RANKL protein was the lymphocyte [2]. We were unable to demonstrate significant OPG or RANKL protein production by type I synoviocytes by immunohistochemistry on synovial tissue.

Finally, the effects of tumour necrosis factor-α (TNF-α) on OPG and RANKL mRNA production shown by Harashima *et al.* are not very impressive and do not appear to correlate with the clinical situation. These authors suggest that TNF-α treatment of RA fibroblasts increased OPG mRNA and decreased RANKL mRNA, yet the active RA synovial fibroblasts (in a clinical situation in which increased TNF-α is expected in the synovial membrane) showed lower OPG and higher RANKL mRNA levels than OA fibroblasts. In addition, this would suggest that anti-TNF treatments would decrease OPG mRNA and increase RANKL mRNA levels in synovial fibroblasts, leading to a situation in which bone erosion should be increased. This is not what clinical trials on anti-TNF treatment have suggested [3].

Perhaps the conclusion that can be drawn is that results from studies undertaken in *in vitro* cell culture systems on isolated cell populations from synovial tissue do not necessarily correlate with what is seen *in vivo* in whole-tissue systems and should be interpreted with caution.

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Statins and lupus erythematosus

Sir, I read with interest the article of Wajed *et al.* [1] regarding the prevention of cardiovascular disease in systemic lupus

erythematosus. Patients with systemic lupus erythematosus (SLE) have a high prevalence of cardiovascular diseases due to premature or accelerated atherosclerosis. Lowering cholesterol levels with statin therapy is one of the main targets in reducing the morbidity and mortality of SLE. However, these lipid-lowering agents may have unexpected immunological effects.

An increasing number of cases of statin-induced lupus like syndrome have recently been reported [2–4]. Most cases were caused by second-generation statins, such as simvastatin and atorvastatin. One case was associated with autoimmune hepatitis [5]. Statins have also been implicated in drug-induced dermatomyositis and other types of autoimmune skin diseases, such as lichen planus pemphigoides [6, 7]. In all cases of statin-induced lupus, skin eruption was similar to that occurring in subacute lupus erythematosus, with positive antinuclear antibodies. Unlike usual drug reactions, the skin eruption was observed only many months after the start of therapy and antinuclear antibodies were still positive many months after drug discontinuation. A causal relationship between drug intake and the autoimmune disease may be therefore difficult to establish.

Two pathogenic mechanisms may be suspected in statin-induced lupus-like syndrome. Cellular apoptosis, which plays a crucial role in SLE, may be exacerbated or triggered by second-generation statins, which are potent pro-apoptotic agents [8]. The release of nuclear antigens into the circulation may foster the production of pathogenic autoantibodies. The same mechanism is implicated with other environmental factors, such as ultraviolet light, which is a well-known triggering factor in SLE. The direct immunomodulator effect of statins on T lymphocytes is possibly also involved. SLE is characterized by a shifting of T helper 1 (Th1) to Th2 immune responses, leading to B-cell reactivity and the production of pathogenic autoantibodies. Statins may aggravate this phenomenon [9, 10].

Statins are among the most widely prescribed drugs. Their overall safety profile is good. However, these drugs have not only cholesterol-lowering properties but also have immunomodulator effects, which may potentially trigger or aggravate autoimmune diseases. Statin-induced lupus must be therefore considered in the differential diagnosis of SLE.

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Reply

We are grateful to Dr Noël, who points out the potential issue of safety of statins, in particular whether they are actually capable of inducing the development of SLE [1]. Firstly, he draws attention to a number of case reports of patients, using a variety of statins, in whom lupus-like syndromes have been reported. It is interesting, given the large volume of prescribing of these agents in Western society, how uncommon these reactions appear to be. In many cases, as the author points out, causation has been difficult to conclusively establish [1].

There are nevertheless theoretical concerns regarding the potential immunomodulatory effects of statins and whether these may aggravate the propensity to develop SLE. In particular, these agents shift the T helper responses towards a Th2 phenotype [2]. While this would again be hypothesized to be detrimental in SLE, it is probably an oversimplification to assume that the pathological features of SLE are entirely driven by a Th2 response. For example, interferon gamma (IFN-γ) appears to have important effects in the context of SLE. Jacobs *et al*. have demonstrated that IFN-γ can exacerbate lupus nephritis [3] and others have noted that a subgroup of relevant nucleosomal histone peptides stimulate IFN-γ production from autoreactive T cells [4]. An important effect of certain statins is to inhibit IFN-γ-induced expression of inducible MHC class II [5]. This reduces subsequent T-cell proliferation and activation. Therefore, statins may actually have potential to attenuate certain immune responses of relevance in SLE.

There is no doubt that premature cardiovascular disease represents a major challenge in the management of SLE patients. There is also no doubt that, in all contexts in which they have been studied, statins have great potential to safely and effectively reduce the burden of cardiovascular disease. As such we recommend their use in the context of SLE where the target LDL cholesterol cannot be achieved by other means [6]. Our initial experience of prescribing statins also suggests that cholesterol reduction can be achieved without any obvious detrimental effects on the underlying SLE. It is also our own view that these agents may actually have a beneficial effect on SLE disease activity, although we acknowledge that it will take a well-designed trial to study in depth their immunomodulatory potential in SLE.

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