of HLA B51, which was notably absent in this family [3]. Studies on the influence of sex and the age of onset on disease severity in BD have shown that young, male patients have more severe disease (including uveitis) than older, female patients [4], a factor that may be relevant in the context of the family reported here.

This family is similar to a Spanish family reported recently in whom three sisters had BD and shared an identical HLA phenotype: A2, B51, Cw6, DR4, Drw53 and Dqw 7 [5]; all six siblings carried the HLA B51 allele. Interestingly, BD only affected females with this phenotype as both the father and one brother also shared this phenotype, but had no features of BD. The authors postulated that the female predominance may be related to hormonal factors.

Previous studies on HLA antigens and BD in Europeans have shown varying results. The HLA B51 allele confers a relative risk for BD of 5.8 in Italy, 7.8 in France and 1.7 in the UK [6]. Correlations have also been shown between BD and DR2 and DR7. DR7 has an association with uveal involvement in British patients [7]; Italian BD patients have increased expression of HLA Drw52 [8]. The prevalence of HLA B5 in the normal Irish population is 2%; the strength of its association with BD in Irish patients is unknown. A 1981 study described the immune status and blood fibrinolytic activity in six Irish BD patients in whom HLA B5 was specifically noted to be absent [9]. This concurs with the findings reported here. In the only other study of Celtic Caucasians that described 15 Scottish patients with BD, five (33%) had severe eye involvement and eight (45%) had significant gastrointestinal (GI) involvement; the overall prevalence of HLA B5 was 12% (2/15) [6]. Three patients with posterior uveitis had HLA DR7 and all of the patients with GI symptoms had either DR4 or DR7. The 33% incidence of eye disease in the Scottish BD patients contrasts with the absence of eye involvement reported here.

In summary, we suggest that the familial incidence of BD in Ireland may not be explained solely on the basis of a susceptible genetic haplotype. The actual contribution of the MHC to the genetic predisposition to BD is unknown and it is possible that multiple minor predisposing genes, in addition to the major MHC, are important in the development of BD. The HLA phenotypes and clinical features in this Irish family are different from those previously reported. The absence of HLA B51, as well as the lack of eye involvement, in these BD patients are notable. BD in Ireland is likely to be clinically and immunogenetically heterogeneous, and may be less severe than that seen in patients from Japan and the Middle East.

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Risk Factors for Thrombotic Events in Giant Cell Arteritis and Polymyalgia Rheumatica

Sm—We read with great interest the article by Manna et al. [1] concerning the relationship between the occurrence of anticyclic lipoprotein antibodies (aCL) in patients with giant cell arteritis (GCA) and/or polymyalgia rheumatica (PMR) at onset and during follow-up. No correlations between ischaemic events and aCL were found, suggesting that the aCL positivity is not an important factor for the development of vascular complications in GCA/PMR patients.

Recent reports on the presence of aCL and the development of thrombotic events during the course of GCA/PMR are discordant [1, 2]. On the other hand, lipoprotein (a) [Lp(a)] has been suggested to be an important risk factor for the vascular complications in patients with other rheumatic diseases [3, 4]. In the light of these observations, we report our recent experience concerning Lp(a) levels in relation to the positivity of aCL and associated thrombotic complications in patients affected by GCA/PMR.

Twenty-eight consecutive patients (20 women, eight men, mean age 71 ± 8 yr, range 62–83 yr) diagnosed as having PMR were included in the study [5]. Twenty patients showed an associated GCA. The diagnosis of GCA was based on the criteria of Hunder et al. [6].

Lp(a) concentrations were detected by ELISA using commercial kits (Terumo Medical Corp., Elkton, MD, USA). Serum IgG and IgM aCL were assayed by ELISA, as previously described (values were expressed as GPL and MPL units) [7]. The mean values (± s.d.) of 86 healthy subjects (15 GPL and 10 MPL units)
were considered as cut-off for both IgG and IgM aCL levels. aCL and Lp(a) levels were determined before and during corticosteroid therapy at 3, 6, 9 and 12 months. Patients were grouped as aCL positive and aCL negative at onset with regard to aCL positivity (see Table I). Twenty-four age- and sex-matched subjects were used as controls (16 women, eight men, mean age 70 ± 7 yr, range 64–80 yr).

The thrombotic events (lasting <1 yr) were carefully assessed by a detailed clinical evaluation. The diagnosis of deep vein thrombosis was confirmed by Doppler ultrasound examination. Cerebral infarction was diagnosed by lesion noted on computed tomography. Retinal arterial thrombosis was diagnosed by fundoscopic examination. The total group of patients with GCA/PMR was found to be affected by a significantly higher rate of venous and arterial thromboses compared to controls [n = 11/28 (39%) vs n = 1/24 (4%), respectively; P = 0.01]. As reported in Table I, thrombotic events were significantly higher in aCL-positive than in aCL-negative GCA/PMR patients and controls.

Lp(a) levels were significantly higher in all patients with GCA/PMR compared to the controls (32 ± 18 mg/dl vs 10 ± 6 mg/ml, respectively; P = 0.001), as well as significantly higher in aCL-positive than in aCL-negative GCA/PMR patients and controls (see Table I). Plasma levels of Lp(a) were significantly higher in aCL-positive GCA/PMR patients with thromboses than in aCL-positive patients without thromboses (54 ± 12 mg/dl vs 26 ± 10 mg/dl; P = 0.01).

Interestingly, Lp(a) concentrations in aCL-positive patients with arterial thromboses were significantly increased when compared to those with venous thromboses (72 ± 10 mg/dl vs 42 ± 11 mg/dl, respectively; P = 0.05).

Before corticosteroid therapy, aCL levels were positive in 13/20 GCA/PMR patients and 3/8 PMR patients. Generally, aCL positivity was of the IgG isotype (mean 52 ± 16 GPL units) in 12 patients and of both IgG and IgM isotype (mean 46 ± 15 GPL units and 38 ± 11 MPL units) in four patients. Furthermore, aCL levels appeared higher in GCA/PMR patients with thromboses than in patients without thromboses (68 ± 18 vs 42 ± 19 GPL units; P = 0.03).

After corticosteroid therapy, aCL levels returned to the normal range in 56% of patients with positive aCL at month 3, in 75% at month 6, in 81% at month 9 and in 87% at month 12. No relationship was found between the concentrations of Lp(a) observed at onset and after corticosteroid therapy in all GCA/PMR patients.

Our data seem to be in agreement with those of Manna et al. [1] confirming the high prevalence of aCL positivity in GCA/PMR patients, whereas we also found a significant correlation between aCL levels and vascular complications. In addition, this study suggests that a large number of GCA/PMR patients with elevated levels of aCL and Lp(a) at onset show an increased risk of developing thrombotic events. Furthermore, the association of increased levels of aCL and Lp(a) might be considered an independent...
The results of several studies have reported that aCL are associated with an increased risk of arterial or venous thrombosis [3, 4]; for this reason, in our study we wanted to point out that thrombotic events in GCA do not seem to be due to aCL activity, but possibly to the vascular inflammation and endothelial alterations by themselves. In this view, we found it very interesting that the authors found higher lipoprotein (a) [Lp(a)] levels in those patients with either aCL or arterial thrombosis, in opposition to those with venous thrombosis. Hypofibrinolysis due to increased Lp(a) levels could promote thrombotic events in the arterial wall damaged by the inflammatory process.

We think that it would be interesting to correlate the incidence of ischaemic events due to arterial thrombosis with Lp(a) levels in a larger population of patients with GCA, and to evaluate the hypothesis that Lp(a) could represent a risk factor for arterial ischaemic events independently from aCL.

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Re: Use of Cyclic Etidronate and the Prevention of Non-vertebral Fractures

Sir—Although the van Staa et al. [1] paper presents interesting observational data on the use of etidronate in post-menopausal osteoporosis, the limitations of this study need to be clearly elucidated. Randomized control trial data are the standard for medical efficacy and side-effects. In the absence of this quality of data, medical regulatory agencies and physicians are reluctant to recommend changes to the care of their patients.

The trial structure is unusual, even for observational data. The criteria for the diagnosis of osteoporosis requiring therapy and for osteoporosis not requiring therapy are not known. Perhaps it would have been clearer to present only the etidronate group, as, in these patients, we do know that a physician has decided that they have osteoporosis and merit therapy.

Between treatment and non-treatment groups, it is not clear whether there has been a significant reduction in the rate of vertebral fractures. However, within the etidronate group, incident vertebral fractures are decreased after a variable period of follow-up. Details on the reasons for discontinuing therapy are not given and we are not sure whether patients remaining on therapy longer might be those who have had more success with therapy. Other measures known to impact upon fracture risk in this group, such as activity, fall prevention, calcium intake and vitamin D nutrition, are not elaborated on.

The non-therapy group were not given therapy for reasons known only to the treating physician. Perhaps they were too frail, had problems ambulating, were less insistent, chose to neglect their health, etc. Any of these factors might increase their risk of future fracture and bias the comparison. If there were adjustments...