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COMMENT ON SYSTEMIC MASTOCYTOSIS STUDY

We read with interest the multicentre study on the use of alpha-interferon (IFN-α) in systemic mastocytosis (SM) (Casassus *et al*, 2002). We would like to make several comments.

Although there was a good response to some symptoms in the group, this was at the expense of significant side-effects. Bone pain appeared to be the most frequent symptom and showed improvement. However, we have found very good symptomatic relief of bone pain with bisphosphonate treatment in three patients with SM. One patient, a 42-year-old man, presented with long-standing and severe, refractory bone pain. Magnetic resonance imaging (MRI) demonstrated highly atypical multifocal marrow abnormalities that were suggestive of widespread metastatic disease. The diagnosis of SM was made after extensive malignancy screening, a repeat MRI and a bone marrow trephine, which was grossly fibrotic with mild myelodysplasia and abnormal mast cells. Monthly pamidronate infusions not only produced significant pain relief, but a repeat MRI after 19 months of treatment also demonstrated the improvement of bone marrow appearance. This was suggestive of a direct effect on mast cell production by the bisphosphonates, analogous to the effect of nitrogen-containing bisphosphonates in myeloma. The stronger bisphosphonate zoledronic acid may be even better in both respects and we are currently carrying out a trial to compare the two. A second patient with SM, a 48-year-old man who presented with pelvic pain, also had widespread MRI abnormalities of both the axial and appendicular skeleton. He has received pamidronate infusions monthly for 4 months, which has led to a good resolution of bone pain. A third patient with bone pain also demonstrated significant pain relief from pamidronate, but unfortunately suffered a delayed allergic reaction (by 12 h), which required admission and steroids to settle. As with all drugs, the possibility of allergic reactions in SM has to be carefully monitored, although the delayed nature of this reaction was unusual. In general, bisphosphonates would appear to be a better option for control of bone pain in SM rather than α-interferon, as the latter has many side-effects that are often similar to the patient's symptoms.

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Keywords: systemic mastocytosis, alpha-interferon, bisphosphonates.

THE CONCOMITANT PRESENCE OF LUPUS ANTICOAGULANT, ANTICARDIOLIPIN AND ANTI-β2-GLYCOPROTEIN I ANTIBODIES COULD BE ASSOCIATED WITH ACQUIRED ACTIVATED PROTEIN C RESISTANCE IN NON-SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

Nojima *et al* (2002) recently reported the co-existence of lupus anticoagulant (LA) and anti-prothrombin antibodies as a risk factor for the prevalence of acquired activated protein C resistance (APCR) in systemic lupus erythematosus (SLE) patients, which was furthermore associated with venous thromboembolism. The acquired APCR phenotype occurs in the absence of the factor V (FV) Leiden mutation and has been described among patients with antiphospholipid antibodies (APA).

There is no clear information about which antibodies are involved in this phenotype. However, an *in vitro* effect of the anti-β2-glycoprotein I (αβ2GPI) antibodies on the response to activated protein C (APC) has been described (Matsuda *et al*, 1995; Martinuzzo *et al*, 1996; Galli *et al*, 1998).

The *in vivo* effect of the APA is less evident. The acquired APCR phenotype has been associated with LA but not with anticardiolipin antibodies (ACA) in children with SLE (Male *et al*, 2001). Our preliminary data in non-SLE patients with LA activity suggest, as stated by Nojima *et al* (2002) for SLE patients, that the sole presence of LA may not be enough to account for the acquired APCR. This is in agreement with the results of Martinuzzo *et al* (1996), showing that a low

Table I. APCR results in the plasma of LA patients without SLE.

		$APCR_{original}$ (NR = 2·40–4·16)			$APCR_{modified}$ (NR = 1·95–3·24)		
Patients	*n*	Abnormal	Mean ± SD	*P*	Abnormal	Mean ± SD	*P*
$ACAIgG^+$ $\alpha\beta2GPIIgG^+$	10	10/10	1·83 ± 0·19	< 0·001	5/10	2·53 ± 0·32	< 0·05
$ACAIgG^-$ $\alpha\beta2GPIIgG^-$	14	0/14	4·14 ± 1·14	< 0·001	0/14	2·88 ± 0·40	< 0·05

NR, normal range.

response to APC seemed to be directly associated with αβ2GPI and/or ACA, irrespective of the presence of another APA, like LA.

We evaluated whether the presence of ACA immunoglobulin (Ig)G and αβ2GPI IgG was associated with acquired APCR in 24 LA patients with primary antiphospholipid syndrome and the following clinical features: venous ($n = 12$) or arterial ($n = 6$) thrombosis and fetal wastage ($n = 6$).

LA was detected in the patients' plasma by the dilute Russell's viper venom time (Sigma) and the activated partial thromboplastin time (aPTT) (PTT-LA; Diagnostica Stago), in addition with mixing studies and neutralization procedures, according to criteria of the Scientific and Standards Committees of the International Society on Thrombosis and Haemostasis. An enzyme-linked immunosorbent assay was performed for the detection of ACA IgG (the binding site) and αβ2GPI IgG (Varelisa; Elias).

Patients were divided into $ACA^+/\alpha\beta2GPI^+$ and $ACA^-/\alpha\beta2GPI^-$ groups. The APCR was evaluated using aPTT-based assays: the original ($APCR_{original}$; Coatest APC resistance-S; Chromogenix) and the modified ($APCR_{modified}$; Coatest APC resistance-V; Chromogenix) tests were performed in order to detect the acquired APCR. The resistance related to FV Leiden or another genetic cause involving FV could affect both systems, unlike the acquired APCR that mainly affects the original test (Gennari *et al,* 2000).

All (10/10) $ACA^+/\alpha\beta2GPI^+$ samples showed abnormal $APCR_{original}$ results, displaying a mean ratio significantly lower than the $ACA^-/\alpha\beta2GPI^-$ group (Table I). A similar pattern, but to a lesser extent, was observed with the $APCR_{modified}$ technique. In five out of 10 samples, the effect on the APC response could not be diluted out (Table I), suggesting that these antibodies may be so 'powerful' that even the dilution in FV-depleted plasma could not normalize the phenotype.

Moreover, an effect of either αβ2GPI or ACA on the protein C pathway could be suspected, as an inverse correlation between the $APCR_{original}$ ratio and the antibody titres ($r_{Spearman}$ αβ2GPI = −0·87; $P < 0·0001$; $r_{Spearman}$ ACA = −0·88; $P = 0·0003$) was found.

Nojima *et al* (2002) showed that the co-existence of antiprothrombin and LA was the most significant risk factor for the prevalence of acquired APCR, but the association of αβ2GPI and LA also appeared to be a significant risk factor. Anti-prothrombin antibodies were not tested in our samples; however, the co-existence of LA with αβ2GPI and ACA in non-SLE patients seemed to be associated with the acquired APCR phenomenon.

In addition to the previous reports, our results suggest that, irrespective of the underlying disease, the presence of different APA may be necessary for the appearance of the acquired APCR phenomenon.

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protein C resistance is associated with the co-existence of anti-prothrombin antibodies and lupus anticoagulant activity in patients with systemic lupus erythematosus. *British Journal of Haematology*, **118**, 577–583.

Keywords: acquired APCR, lupus anticoagulant, ACA IgG antibodies, antiβ2GPI IgG antibodies, non-SLE patients.

HIGH INCIDENCE OF LYMPHOMAS IN A SUBGROUP OF WISKOTT–ALDRICH SYNDROME PATIENTS

We read with interest the report of Inoue *et al* (2002) describing Wiskott–Aldrich syndrome (WAS) caused by the intron 6 (+ 5), g → a mutation of the *WASP* gene in several members of one family, including a girl. In the Wiskott–Aldrich syndrome, the course of disease varies from the full-blown disorder, characterized by profound thrombocytopenia, immunodeficiency, eczema, autoimmune pathology and tumours, especially B-cell lymphomas (Sullivan *et al*, 1994), to thrombocytopenia with or without mild immunodeficiency (also called X-linked thrombocytopenia or XLT) (Ochs, 1998) as found in the family described by Inoue *et al* (2002). We wish to comment on additional kindred who have this splice site mutation (Kwan *et al*, 1995; Zhu *et al*, 1997; Lemahieu *et al*, 1999; Shcherbina *et al*, 1999), and call attention to the unusual effect of the mutation at the cell level and the surprising and worrisome phenotype. The unfortunate feature of the intron 6 (+ 5), g → a mutation compared with other *WASP* mutations associated with mild disease seems to be the high frequency of B-cell lymphomas that develop when the patients are young adults (Shcherbina *et al*, 1999).

To test our initial observations on lymphoma frequency, we assembled data for WAS patients with known mutations. Table I includes information from published reports as well as responses to questionnaires distributed to clinician researchers known to care for WAS patients (18 responses to 33 inquiries). Although there is not strict correlation between the nature of the mutation and disease severity, missense mutations, especially the frequent mutations in exons 1–3, generally lead to mild disease, whereas nonsense and frameshift mutations, expected to lead to WASP-negative cells, are associated with more severe disease.

For the 158 kindred with known missense mutations, cases of lymphoma were reported for five kindred (3·2%) (Table I). Among the 163 kindred with nonsense and frameshift mutations, lymphoma cases were reported for 15 kindred (9·2%). For this group, the observed lymphoma frequency probably underestimates the true susceptibility because many severe phenotype patients undergo early

Table I. Incidence of lymphoma in WAS kindred with different types of mutations.
(A) Detailed distribution.

	Missense mutations		Splice site mutations	
Exon/intron	Total kindred	Kindred with lymphoma case(s)	Total kindred	Kindred with lymphoma case(s)
1	20		2	
2	91	2	2	
3	10	3	6	
4	25		2	
5	0		0	
6	1		9	4
7	1		6	
8	0		16	3
9	2		4	
10	1		5	
11	7		6	
12	0		0	

(B) Summary of distribution.

Missense mutations		Nonsense and frameshift mutations		Splice site mutations	
Total kindred	Kindred with lymphoma	Total kindred	Kindred with lymphoma	Total kindred	Kindred with lymphoma
158	5 (3·2%)	163	15 (9·2%)	58	7 (12·1%)