Heparin-dependent and -independent anti-platelet factor 4 autoantibodies in patients with systemic lupus erythematosus

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Abstract

Objective. Antibodies that recognize complexes formed by platelet factor 4 (PF4) and heparin are involved in the pathogenesis of heparin-induced thrombocytopenia (HIT). This study was undertaken to investigate the prevalence and clinical correlations of anti-PF4 autoantibodies in patients with SLE.

Methods. We studied 118 patients with SLE, 78 with primary immune thrombocytopenia (ITP), 27 with primary APS, 2 with HIT (as positive controls) and 47 healthy controls. Heparin-dependent and -independent anti-PF4 antibodies were measured with an ELISA. Antibody binding was confirmed to be heparin-dependent when inhibited by the presence of a high concentration of heparin. Pathogenic anti-PF4 antibody was assessed by serotonin-release assay.

Results. Heparin-dependent anti-PF4 antibodies were detected in 11 SLE (9%) and 2 primary ITP (3%) patients, but at much lower levels than in HIT patients. In serotonin-release assays, only the HIT sera induced platelet activation in vitro. Heparin-independent anti-PF4 antibodies were detected in 17 SLE patients (14%). There was no correlation between the levels of heparin-dependent and -independent anti-PF4 antibodies. Cross-reactivity between these two antibodies was not detectable by ELISA competitive assay. Heparin-dependent anti-PF4 antibodies were associated with thrombocytopenia and IgM aCLs (P = 0.007 for both comparisons), while heparin-independent anti-PF4 antibody levels were correlated with SLE disease activity index (P = 0.0005). None of the SLE patients with anti-PF4 antibodies had previous heparin exposure.

Conclusion. PF4 is an autoimmune target in SLE patients. Heparin-dependent and -independent anti-PF4 autoantibodies may be involved in different aspects of pathophysiology of SLE.

Key words: autoantigens and autoantibodies, systemic lupus erythematosus and autoimmunity, haematopoietic, laboratory diagnosis, immunological techniques.

Introduction

Heparin-induced thrombocytopenia (HIT) is an immunemediated disorder that can develop during anticoagulation therapy with heparin, particularly unfractionated heparin [1]. Approximately 25% of patients with HIT paradoxically develop arterial and/or venous thrombosis. HIT is associated with antibodies that recognize oligomeric complexes formed between platelet factor 4 (PF4) and heparin or endogenous heparinoids, such as GAGs [2]. There is increasing evidence that immune complexes formed by IgG antibodies and the PF4–heparin complex bind to FcγRIIA receptors on platelets, activating the platelets and accelerating the coagulation pathway by generating thrombin [2]. These heparin-dependent anti-PF4 antibodies recognize neoepitopes formed on the PF4–heparin complex, and are a hallmark of HIT. Recently heparin-dependent anti-PF4 antibodies were also documented in individuals without clinical HIT or previous heparin exposure [3–7]. Several studies have
demonstrated that heparin-dependent anti-PF4 antibodies are present in 4–15% of patients with SLE or APS [5, 6]; however, Pauzner et al. [8] reported that the majority of such patients actually had antibodies reactive with PF4 alone, or heparin-independent anti-PF4 antibodies. These findings suggest that PF4 may be targeted by autoantibody responses in systemic autoimmune diseases. Despite the definitive role of heparin-dependent anti-PF4 antibodies in the pathogenesis of HIT, the clinical relevance of naturally occurring anti-PF4 autoantibodies, heparin-dependent or -independent, in SLE patients remains unclear. Some authors have postulated that heparin-dependent anti-PF4 antibodies may represent an additional prothrombotic risk for APS [7, 9], whereas another report failed to reproduce this association [6].

In this study we examined heparin-dependent and -independent anti-PF4 antibodies in patients with SLE, primary APS and primary immune thrombocytopenia (ITP), conditions that share clinical features in whole or in part with HIT, and evaluated associations between antibody specificities and clinical characteristics, including thrombocytopenia and thromboembolism.

**Materials and methods**

**Patients and controls**

We studied 118 patients with SLE, 78 with primary ITP and 27 with primary APS, who were seen at Keio University Hospital, Tokyo, Japan. Forty-seven healthy volunteers were used as a control. None of the subjects had a current or previous diagnosis of HIT. Plasma samples from two patients diagnosed with HIT were used as a positive control for the anti-PF4 antibody assays. All patients with SLE fulfilled the ACR preliminary classification criteria [10]. Primary ITP was defined as isolated thrombocytopenia (platelet count <100 × 10^9/l) with a normal peripheral blood smear and no underlying conditions that could account for the thrombocytopenic state [11]. Patients meeting the revised Sapporo criteria were categorized as APS [12], and APS patients without underlying immunological diseases such as SLE were categorized as having primary APS. All samples were collected after patients and control subjects gave informed, written consent according to the Declaration of Helsinki. This study has been approved by the Keio University Institutional Review Board.

**Clinical features of SLE patients**

Demographic and clinical information was obtained from all SLE patients by retrospective chart review at the time blood samples were collected. Thirty-seven clinical and laboratory findings observed during the entire disease course were recorded; these were individual items included in the ACR preliminary classification criteria [10] and the SLEDAI [13], as well as any history of thromboembolism, fetal loss or previous heparin exposure. The SLEDAI was calculated at the time of blood sampling.

**Autoantibody assays**

IgG aCL and IgM isotypes were assayed by a commercial ELISA kit (MBL, Nagoya, Japan). LA was determined by a cross-mixing test using a commercially available kit based on the dilute Russell’s viper venom test (Gradipore, Sydney, Australia). Anti-dsDNA antibody levels were measured by a commercial ELISA kit (MBL). Antibody response to GPIIb/IIIa, a major platelet antigen recognized by anti-platelet antibodies in ITP patients, was evaluated by an enzyme-linked immunospot assay for circulating B cells producing IgG anti-GPIIb/IIIa antibodies [14].

**Detection of heparin-dependent anti-PF4 antibodies**

Heparin-dependent anti-PF4 antibodies were measured using an ELISA kit for anti-PF4-heparin antibodies (GTI, Waukesha, WI, USA) with a microtiter plate coated with a complex of PF4 and polyvinylsulphonate, and anti-IgG/A/M secondary antibodies, according to the manufacturer’s protocol. Polyvinylsulphonate is an anionic polymer that provides a high density of negative charges and mimics unfractionated heparin. Samples were tested in duplicate. Antibody units were calculated from optical density read at 450 nm (OD_450) using a standard curve obtained from serial concentrations of an HIT serum containing a high titre of heparin-dependent anti-PF4 antibodies. The cut-off level represented the mean plus four times the s.d. of 30 healthy individuals (3.3 U). To confirm that antibody binding was heparin-dependent, sera were applied to the PF4-heparin ELISA in the presence or absence of a high concentration of unfractionated heparin (100 U/ml); this disrupts the PF4-heparin complex, such that its antigenicity for heparin-dependent anti-PF4 antibodies is lost [15]. Results were expressed as an inhibition rate (%) calculated according to the following formula: 100 × (1 − sample OD_450 in the presence of heparin/sample OD_450 in the absence of heparin). An inhibition rate exceeding 40% was regarded as significant, based on previous reports [15, 16]. Patients were considered positive for heparin-dependent anti-PF4 antibodies when the results from both the PF4-heparin ELISA and the confirmatory heparin inhibition assay were positive.

**Detection of heparin-independent anti-PF4 antibodies**

Heparin-independent anti-PF4 antibodies were measured by an ELISA system, that was developed based on a previously described strategy [17]. Briefly, polyvinyl 96-well plates were coated with human PF4 (ARP, Belmont, MA, USA) at 0.5 μg/ml and blocked with 3% BSA. The wells were incubated with plasma samples diluted at 1:50, and subsequently with peroxidase-conjugated goat anti-human IgG/A/M (ICN/Cappel, Aurora, OH, USA). All samples were tested in duplicate. Antibody units were calculated from the OD_450 using a standard curve obtained from serial concentrations (0.0625 – 4 μg/ml) of rabbit anti-human PF4 polyclonal antibodies (Chemicon International, Temecula, CA, USA) and peroxidase-conjugated goat...
anti-rabbit IgG secondary antibodies (ICN/Cappel). One unit of heparin-independent anti-PF4 antibody was defined as 0.625 μg/ml of rabbit anti-human PF4 antibody. The cut-off value was the mean plus four times the s.d. of 30 healthy individuals (7.4 U).

Serotonin-release assay
The functional capacity of heparin-dependent anti-PF4 antibodies to activate platelets in vitro was assessed by a serotonin-release assay as described elsewhere [7]. Briefly, platelet-rich plasma from healthy individuals was incubated with [14C]serotonin (0.1 μCi/ml; Amersham Biosciences, Uppsala, Sweden), and then with the patient’s heat-inactivated plasma in the presence of unfracti

Statistical analysis
Continuous variables were shown as the mean (s.d.). Differences between two groups were tested for statistical significance using the chi-square test or Fisher’s two-tailed exact test where applicable, or the non-parametric Mann–Whitney U-test. The odds ratio (OR) with a 95% CI was calculated for a statistically significant difference. The correlation coefficient was obtained by Spearman’s correlation analysis.

Results
Heparin-dependent anti-PF4 antibodies in SLE
We used a PF4–heparin ELISA to screen for heparin-dependent anti-PF4 antibodies in 118 patients with SLE, 78 with primary ITP, 27 with primary APS, 2 with HIT and 47 healthy controls (Fig. 1A). Heparin-dependent anti-PF4 antibodies were detected in 13 patients with SLE (11%) and 2 with primary ITP (3%), but not in any healthy controls or patients with primary APS. Sera from two HIT patients showed remarkably high levels of heparin-dependent anti-PF4 antibodies, suggesting that the antibody titres produced in patients with SLE or primary ITP were low. To confirm that the antibody binding was heparin-dependent, the 17 sera that were positive for heparin-dependent anti-PF4 antibodies by the PF4–heparin ELISA were subjected to a confirmatory heparin inhibition assay (Fig. 1B). In all but two SLE sera, the antibody reactivity was significantly suppressed in the presence of a high heparin concentration. As a result, 11 patients with SLE (9%) were judged to have heparin-dependent anti-PF4 antibodies.

We further evaluated the capacity of the heparin-dependent anti-PF4 antibodies to promote in vitro platelet aggregation in the presence of a therapeutic concentration of heparin (0.1 U/ml). The 11 SLE sera positive for heparin-dependent anti-PF4 antibodies were applied to this assay, while 13 randomly selected SLE sera negative
for heparin-dependent anti-PF4 antibodies were used as a reference. As shown in Fig. 2A, only one of the ELISA-negative sera had a positive (quite weak) reaction. However, this reactivity was not inhibited by a high heparin concentration (100 U/ml) (Fig. 2B), indicating that none of these SLE sera, including the ones with positive PF4-heparin ELISA results, exerted functional properties in the serotonin-release assay. In contrast, the two HIT sera strongly promoted in vitro platelet activation in the presence of a low heparin concentration, and this reactivity was inhibited in the presence of a high heparin concentration.

Correlation between heparin-dependent and -independent anti-PF4 antibodies

ELISA using PF4 antigen in the absence of heparin found heparin-independent anti-PF4 antibodies in 17 (14%) of 118 SLE patients, but in none of the 47 healthy controls. Fig. 3A shows the distribution of heparin-dependent and -independent anti-PF4 antibody levels in the 118 patients with SLE; there was no correlation between the levels of the two antibodies ($r^2 = 0.04$). Twelve (71%) of 17 patients positive for the heparin-independent antibody gave a negative result in ELISA for the heparin-dependent antibody. Only five patients had positive ELISA values for both antibody specificities, but two of them were found to have false-positive PF4-heparin ELISA results [8] because the confirmatory heparin inhibition assay was negative.

To further evaluate the specificity of heparin-dependent and -independent anti-PF4 antibodies, ELISA competition assays were performed using PF4 as a competitor (Fig. 3B and C). Heparin-dependent anti-PF4 antibody reactivity was not inhibited by pretreatment of plasma samples with serial concentrations of human PF4. In contrast, heparin-independent anti-PF4 antibody reactivity was inhibited by PF4 in a dose-dependent manner. This discordant finding was obtained from two patients positive for both heparin-dependent and -independent anti-PF4 antibodies.
antibodies (closed circles and squares). Thus the repertoires of anti-PF4 autoantibodies detected by heparin-dependent and -independent ELISA are essentially separate.

Clinical features of SLE patients with heparin-dependent or -independent anti-PF4 antibodies

Demographic and clinical features were compared between SLE patients with and without heparin-dependent anti-PF4 antibodies (Table 1). Thrombocytopenia was more frequently detected in patients with heparin-dependent anti-PF4 antibody than in those without (46 vs 12%; \( P = 0.007; \) OR = 6.0; 95% CI 1.6–22.6). All five patients with thrombocytopenia had circulating B cells producing IgG anti-GPIIb/IIIa antibodies. There was no difference in the frequency of IgG aCL or LA, but IgM aCL was more common in patients with heparin-dependent anti-PF4 antibody than in those without (64 vs 25%; \( P = 0.007; \) OR = 5.2; 95% CI 1.4–19.1). The frequencies of other clinical and serological features, including thromboembolism and fetal loss, were similar between the two groups. In addition, SLEDAI at blood sampling was comparable. There was no correlation between the heparin-dependent anti-PF4 antibody level and SLEDAI. Interestingly, a previous history of heparin exposure was found solely in a small proportion of patients who did not have heparin-dependent anti-PF4 antibodies.

Table 1 Demographic and clinical features of SLE patients with and without heparin-dependent anti-PF4 antibodies

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Heparin-dependent anti-PF4 antibody</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>Positive (( n = 11 ))</td>
<td></td>
</tr>
<tr>
<td>Sex, % female</td>
<td>91</td>
<td>92</td>
</tr>
<tr>
<td>Age at SLE onset, years</td>
<td>38.4 (8.9)</td>
<td>41.8 (13.6)</td>
</tr>
<tr>
<td>Malar rash, %</td>
<td>36</td>
<td>62</td>
</tr>
<tr>
<td>Discoid rash, %</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Photosensitivity, %</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Oral ulcers, %</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Arthritis, %</td>
<td>82</td>
<td>64</td>
</tr>
<tr>
<td>Serositis, %</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Renal disorder, %</td>
<td>18</td>
<td>38</td>
</tr>
<tr>
<td>Haemolytic anaemia, %</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Neurological disorder, %</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Leucopenia, %</td>
<td>64</td>
<td>59</td>
</tr>
<tr>
<td>Lymphopenia, %</td>
<td>55</td>
<td>51</td>
</tr>
<tr>
<td>Thrombocytopenia, %</td>
<td>46</td>
<td>12</td>
</tr>
<tr>
<td>Anti-dsDNA antibody, %</td>
<td>73</td>
<td>82</td>
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<tr>
<td>Anti-dsDNA antibody level, units</td>
<td>72.1 (113.5)</td>
<td>61.3 (75.6)</td>
</tr>
<tr>
<td>IgG aCL, %</td>
<td>36</td>
<td>45</td>
</tr>
<tr>
<td>IgM aCL, %</td>
<td>64</td>
<td>25</td>
</tr>
<tr>
<td>LA, %</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Thromboembolism, %</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td>Fetal loss, % (( n+)/( n ))</td>
<td>14 (1/7)</td>
<td>14 (6/42)</td>
</tr>
<tr>
<td>Secondary APS, %</td>
<td>27</td>
<td>17</td>
</tr>
<tr>
<td>History of heparin exposure, %</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>3.3 (2.9)</td>
<td>3.7 (5.0)</td>
</tr>
</tbody>
</table>

Values are represented as the mean (s.d.), unless otherwise indicated.

On the other hand, there was no difference in the clinical and serological features during the entire disease course between SLE patients stratified by the presence or absence of heparin-independent anti-PF4 antibodies. However, SLEDAI at blood sampling was significantly higher in patients with heparin-independent anti-PF4 antibodies than in those without [10.9 (6.1) vs 2.5 (3.4); \( P < 0.0001 \)]. Anti-dsDNA antibody levels did not differ between heparin-independent anti-PF4 antibody-positive and -negative groups [80.9 (82.6) vs 59.1 (78.7); \( P = 0.29 \)]. Heparin-independent anti-PF4 antibody levels were positively correlated with SLEDAI (\( P = 0.0005, \ r^2 = 0.51 \)) (Fig. 4). Levels of anti-dsDNA antibody, which is known as a marker for disease activity in SLE, were also correlated with SLEDAI (\( P = 0.003, \ r^2 = 0.35 \)). Interestingly, levels of heparin-independent anti-PF4 and anti-dsDNA antibodies were not correlated with each other (\( r^2 = 0.05 \)). Again, none of the patients with heparin-independent anti-PF4 antibodies had previous heparin exposure.

Discussion

In the present study we found autoantibodies against PF4, either associated with heparin or not, in a significant proportion (\( \sim 19\% \)) of patients with SLE. Heparin-dependent and -independent anti-PF4 antibody specificities were principally separate. The production of heparin-dependent anti-PF4 antibodies was not linked to previous
heparin exposure or to typical clinical HIT features, but was associated with thrombocytopenia and IgM aCL. On the other hand, heparin-independent anti-PF4 antibody levels were correlated with lupus activity measured by SLEDAI.

In our assay systems, repertoires of heparin-dependent and -independent anti-PF4 antibodies appeared to be separate, since (i) levels of these two antibodies did not correlate at all; and (ii) ELISA competition assay indicated no cross-reactivity between free PF4 and PF4 bound to anionic polymer surfaces. It has been reported that heparin-dependent anti-PF4 antibodies detected in patients with HIT recognize ultra-large complexes of PF4 and heparin, but do not react with PF4 in its free form [19]. PF4 binds with high affinity to the negatively charged surfaces, resulting in a dramatic change in its conformation [20]. The precise mechanisms for lack of heparin-independent anti-PF4 antibody reactivity in the PF4–heparin ELISA remain unclear, but the epitope(s) recognized by heparin-independent anti-PF4 antibodies may be masked by competition with heparin for the binding site and/or lost by the conformational change of PF4.

The relatively low prevalence of heparin-dependent anti-PF4 antibodies in our cohort of SLE patients (9%) was nearly concordant with previous studies, in which the prevalence was 4–15% [5, 6]. In the majority of sera with positive PF4–heparin ELISA results, the antibody reactivity was inhibited in the presence of a high heparin concentration, indicating the heparin-dependent nature of the antibody binding. However, none of these sera tested positive by the serotonin-release assay, a gold standard functional assay for diagnosing HIT. This was probably due to the relatively low antibody titres found in patients with SLE, since the ELISA system is more sensitive than the serotonin-release assay [21]. Interestingly, the incidence of heparin-dependent anti-PF4 antibodies is surprisingly high in patients exposed to heparin, exceeding a quarter of all exposed patients, although only a small portion of these patients develop HIT [22]. Antibody titre has been shown to be one of the factors determining whether individuals with heparin-dependent anti-PF4 antibodies remain asymptomatic or develop HIT [23]. Alternatively, the apparent discrepancy between the ELISA and serotonin-release assays might be explained by a lack of heparin-dependent anti-PF4 antibodies of the IgG isotype in SLE sera, since in vitro platelet activation is mediated through IgG antibodies that bind to the heparin–PF4 complex and cross-link with FcγRIIA receptors expressed on platelet surfaces [24]. In this regard, it has been reported that the predominant isotype found in heparin-dependent anti-PF4 antibodies in SLE patients is IgM [7], which does not interact with the FcγRIIA receptor.

In our cohort, the only clinical feature associated with the presence of heparin-dependent anti-PF4 antibodies was thrombocytopenia, although this association has not been described in previous studies [6, 7]. The presence of the anti-GPIIb/IIIa autoantibody response we observed in thrombocytopenic patients with heparin-dependent anti-PF4 antibodies strongly suggests that the thrombocytopenia is caused mainly by anti-platelet autoantibodies to GPIIb/IIIa that accelerate platelet clearance through the reticuloendothelial system (the pathogenic process in ITP) rather than by the consumption of platelets through their activation and the acceleration of the coagulation pathway (the pathogenic process in HIT). Since the PF4 protein is stored abundantly in platelet granules, it is possible that heparin-dependent anti-PF4
antibodies are produced simply as a consequence of excessive platelet destruction. The presence of heparin-dependent anti-PF4 antibodies in some patients with primary ITP supports this hypothesis.

In contrast, the presence of heparin-independent anti-PF4 antibodies was associated with SLE disease activity. Interestingly, there was no correlation between levels of heparin-independent anti-PF4 and anti-dsDNA antibodies, suggesting that measurement of heparin-independent anti-PF4 antibodies together with anti-dsDNA antibodies may provide additional information useful in evaluating disease activity in SLE patients. A circulating level of PF4 is maintained in a very low level (≤20 ng/ml), because PF4 released by activated platelets rapidly disappears from circulation by binding to endogenous heparinoids expressed on endothelial cells [25]. In patients with active SLE, vascular inflammation and resultant endothelial injury in affected tissues, such as kidney and central nervous system, may lead to local release of an excessive amount of PF4 from activated platelets and damaged endothelium. In this case, circulating heparin-independent anti-PF4 autoantibodies may accelerate vascular damage by forming immune complexes by binding to free PF4.

In contrast to a previous report by Alpert et al. [7], we did not observe an association between heparin-dependent anti-PF4 antibodies and thromboembolism or an APS diagnosis. In addition, heparin-dependent anti-PF4 antibodies were not detected in any patients with primary APS. The discrepancy in these results may be due to the small number of APS patients enrolled in our study. On the other hand, our study reproduced a significant correlation between heparin-dependent anti-PF4 antibodies and IgM aCL reported by Alpert et al. A partial cross-reactivity between heparin-dependent IgM anti-PF4 antibody and IgM aCL may be responsible, in part, for this relationship [7, 26].

None of the SLE patients with heparin-dependent anti-PF4 antibodies had developed clinical HIT at the time of this study, but the presence of this autoantibody may be clinically important. In individuals with a history of HIT and low-titre heparin-dependent anti-PF4 antibodies, HIT frequently recurs upon re-exposure to heparin [27]. In addition, preexisting heparin-dependent anti-PF4 antibodies without previous heparin exposure increases the risk of developing HIT following an invasive procedure requiring heparin use [28, 29]. Taken together, it is likely that SLE patients with low-titre heparin-dependent anti-PF4 antibodies may also have an increased risk for developing HIT when treated with heparin. In this regard, a recent retrospective cohort study of 25,653 patients receiving heparin products found a strong correlation between autoimmune diseases, such as SLE, and the development of HIT [30]. Thus SLE patients with heparin-dependent anti-PF4 autoantibodies should be watched closely for signs of developing HIT, when they are given heparin products.

The mechanisms by which anti-PF4 autoantibodies are produced without heparin exposure in SLE patients remain unclear. Since anti-PF4 antibodies in SLE sera apparently recognize multiple epitopes formed on the PF4–heparin complex as well as on PF4 alone, PF4 itself appears to be a preferred target of the autoimmune response. In this regard, three patients who suffered acute-onset arterial thrombosis and thrombocytopenia with heparin-dependent anti-PF4 autoantibodies despite a lack of previous heparin exposure have been reported [31], suggesting that HIT can present as an autoimmune disease. Given that the presence of autoimmune and inflammatory conditions is a risk factor for developing HIT [30], the vascular inflammation observed in SLE patients may trigger an autoantibody response to PF4 through the release of large amounts of PF4 from platelets, followed by the formation of the antigenic complex with endogenous heparinoids [32]. In addition, a predisposition to autoimmunity in SLE patients may also promote an autoantibody response.

In summary, PF4 is an autoimmune target in patients with SLE. Interestingly, heparin-dependent and -independent anti-PF4 autoantibodies may be involved in different aspects of pathophysiology of SLE. Further prospective studies are needed to evaluate whether heparin-dependent anti-PF4 antibodies preexisting in SLE patients increase their risk of developing HIT when exposed to heparin and whether heparin-independent anti-PF4 antibodies are useful as a biomarker for lupus activity.

Rheumatology key messages

- Low heparin-dependent anti-PF4 autoantibody titres are present in some SLE patients.
- Heparin-dependent anti-PF4 antibodies are associated with thrombocytopenia and IgM aCLs.
- Heparin-independent anti-PF4 antibody levels are correlated with lupus activity.

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References


