that the lupus flare might have been due to the initial underdosing of cyclophosphamide. This explanation is plausible, but we would like to say that lupus flares can occur during or after stopping CPM treatment, suggesting the possible pathomechanisms of lupus flare.

In the immunological test after the first treatment of IV CPM, the patient had increased C3 level, but C4 was decreased. According to a previous study by Ho, et al.[2], a decrease in C4 was associated with a concurrent increase in renal disease activity ($p = 0.02$). A decrease in C4 was especially associated with concurrent decreases in the hematocrit levels ($p = 0.009$), and previous increases in C3 were also associated with a higher frequency of decrease in platelet counts ($p = 0.02$). These data show that the renal and hematologic systemic lupus erythematosus (SLE) activity and flares are strongly associated with decreased C4.

Recently, Finke, et al.[3] demonstrated that complement C4-deficient mice result in elevated intravascular levels of apoptotic DNA, targeted to the splenic marginal zone where it accumulates and induces type I interferon-gamma (IFN-γ). Type I IFN-γ is important for the initiation and potentiation of SLE activity and correlated with the renal disease and the presence of cutaneous manifestations[4].

Therefore, we suggest that CPM is not an inducer but an inhibitor of lupus flare, and decreases in C4 and increased type I IFN-γ might play the central role in the development of lupus activity and flares. However, further studies are necessary to elucidate the exact molecular roles of complement deficiency and elevated levels of IFN-γ. The potential therapeutic antibodies directed to either type I IFN-γ or IFN α chain of the receptor 1 (IFNAR1)/IFNAR2 should also be further evaluated in the future.

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Flare lupic during induction with cyclophosphamide therapy in diffuse proliferative lupus nephropathy

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To the Editor,

With regards our scientific letter, "Cyclophosphamide-induced lupus flare in diffuse proliferative lupus nephropathy"[1] we would like to thank Park at al for their contribution, and their suggestions of the possible immunological mechanisms involved in a lupus flare. Although they question whether cyclophosphamide really induces the flare or whether other mechanisms are involved, we would like to clarify that the title of the English version "Cyclophosphamide-induced lupus flare" could lead readers to believe that we consider that treatment with cyclophosphamide induced the flare, however, we wanted to communicate exactly the opposite. Indeed, as was reflected in the "Discussion" section, cyclophosphamide treatment is the best immunosuppressive agent, with the best results in inducing remission in severe forms of lupus nephropathy (LN).[2] As Park at al have pointed out in their letter, the lupus flare may or may not occur after cyclophosphamide treatment. In our case, it was during the cyclophosphamide induction period (less than 15 days). The flare was confirmed following the first phosphamide dose. Therefore, after having dismissed several causes (renal vein thrombosis, infection, etc.), we brought another cyclophosphamide dose forward (the second dose was 1.5g), which caused clinical and biochemical improvements, and the patient went into remission. To date, the patient has not had any further flares. We would like to emphasise the importance of the cyclophosphamide administered: we used the Euro-Lupus Nephritis Trial regime, 500mg every 15 days.[3] In this patient the flare would have been earlier, since the relapse occurred less than 15 days with 1g of the first dose of cyclophosphamide. For that reason, before considering cyclophosphamide treatment to be ineffective, it is important to bear in mind the dose that has been administered. Finally, we must highlight that we did not consider for one moment that cyclophosphamide induced the lupus flare. Given an error in the English version, the English title should have been: *Flare lupic during induction with cyclophosphamide therapy in diffuse proliferative lupus nephropathy.*

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B) BRIEF PAPERS ON RESEARCH AND CLINICAL EXPERIMENTS

Metformin-induced lactic acidosis: usefulness of measuring levels and therapy with high-flux haemodialysis

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To the Editor,

Lactic acidosis in metformin-treated diabetes mellitus patients is a very rare complication, with a high mortality rate and is often associated with an underlying condition, which alone could cause this very severe hydroelectrolytic imbalance. Metformin is a widely-used oral antidiabetic agent, which is eliminated by active tubular secretion, but accumulates in patients with kidney failure.[1] Clinically, metformin-associated lactic acidosis (MALA) develops abruptly and is accompanied by overbreathing, abdominal pain, drowsiness and coma. Abnormal laboratory MALA indicators are a high anion gap, base excess in the arterial blood gas and high plasma lactate levels (prognostic value) and metformin plasma levels. Monitoring the lactate and metformin levels is a very useful way of evaluating the evolution and the possible modifications in the treatment. MALA treatment is controversial; using bicarbonate is usual although there is no scientific evidence associating it with a better prognosis. Low metformin binding to plasma proteins allows haemodialysis techniques with bicarbonate solutions to be used when it has been overdosed. This technique has proven to be effective in eliminating plasma metformin and also allows acidosis to be corrected.[2,3] Dialysis seems to contribute significantly to treating this severe pathology and improving results where MALA is associated with acute renal failure.[4] If we were to compare MALA to severe lactic acidosis located elsewhere, MALA prognosis is significantly better. Its diagnosis should be considered in all metformin-treated patients that present with lactic acidosis.[5]

Eighty-one year old patient with high blood pressure, dyslipidaemia, type 2 diabetes and dilated myocardiopathy (ejection fraction [EF] 30%). Usual treatment: telmisartan, torsemide, metformin 850mg/8hrs, atorvastatin, carvedilol and omeprazole. She arrived at the emergency department with diarrhoea with mucus and blood, and vomiting, which had lasted for one week, as well as oligoanuria for 24 hours.

Physical examination: blood pressure: 120/70mm Hg, heart rate (HR): 95bpm, temperature (T): 36ºC.

Neurological examination: Glasgow score 12, time/space disorientation and bradypsychia, with no signs of focusing. Rhythmic heart beat, no murmur, crackling until the middle field. No signs in the abdomen and lower limbs.

Biochemical tests showed: haemoglobin: 11.7g/dl; leukocytes: 18 030 (78.9% neutrophils); platelets: 307 000; glucose: 68mg/dl; urea: 133mg/dl; creatinine: 6.89mg/dl; sodium: 134mEq/l; potassium: 4.4mEq/l; pH: 6.89; pCO_2: 29mm Hg; bicarbonate: 6.9mmol/l; ionic calcium: 3.85mg/dl; anion gap: 28. Normal coagulation. Urine: pH: 6; creatinine: 71mg/dl; proteinuria: 400mg/dl; 100 red blood cells/field; 60 leukocytes/field; positive ketone bodies and negative drugs (benzodiazepines, barbiturates). Normal abdominal ultrasound with symmetrical kidneys (12cm); good corticomedullary delimitation.

Electrocardiogram: left bundle branch block (LBBB) at 93bpm. Chest X-ray: cardiomegaly and normal cranial computerised tomography (CT). She was diagnosed with stage 2 chronic kidney failure secondary to acute prerenal hypertensive and diabetic nephropathy in a tubular necrosis phase and high anion gap lactic metabolic acidosis. Repletion treatment with physiological saline solution (PSS) at 0.9%, and dextrose solution at 5%, loop diuretics and 1M sodium bicarbonate. Despite this treatment, she continued with anuria and her cognitive function continued to