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F. Levy[1], V. Camarero Temiño[1], A. Blasco Mollá[2], M.P. Ortega Lafont[2], P. Abaigar Luquin[1], M.J. Izquierdo Ortiz[1], G. Torres Torres[1]

[1] Nephrology Department.
Healthcare Complex of Burgos, Spain
[2] Microbiology Department.
Healthcare Complex of Burgos, Spain
Correspondence: F. Levy
Servicio de Nefrología.
Complejo Universitario Asistencial de Burgos.
federicolevy@yahoo.com.ar

Intraperitoneal daptomycin

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To the Editor,

Peritonitis is one of the main causes of morbidity in patients undergoing peritoneal dialysis (PD). Although the usual treatments with vancomycin, aminoglycosides or semi-synthetic penicillins recommended in treatment guidelines for peritonitis[1] are efficient in most cases, situations such as colonisation by methicillin-resistant microorganisms with some degree of resistance to vancomycin are common. These treatments are ineffective in these cases.

The proliferation of multi-resistant gram-positive pathogens has led to the antibiotic daptomycin being brought back and its clinical development has started again. It was approved by the United States Food and Drug Administration (FDA) in 2003 for the treatment of endocarditis caused by gram-positive pathogens, and skin and white-tissue infections.

A case study has been published of peritonitis which was not linked to the peritoneal catheter that was treated with intravenous daptomycin. This study analysed the concentration of daptomycin reached in the peritoneal fluid after intravenous administration. It was found to be 5mg/ml (minimum inhibitory concentration [MIC]=4mg/ml).[2] Therefore, the concentrations in the intraperitoneal fluid as a result of intraperitoneal administration of the antibiotic would be less close to the microorganism MIC for daptomycin.

The clinical experience published to date is limited to two cases. Intraperitoneal daptomycin was used in these cases to treat peritonitis caused by vancomycin-resistant gram-positive bacteria.[3] This treatment succeeded in these cases where conventional therapies had previously failed. The intraperitoneal administration of daptomycin was well tolerated in these patients and they had no peritoneal irritation or negative effects associated with the administration of drugs through this route.

Furthermore, daptomycin is a drug that is currently used to treat catheter-related bacteriaemias[4] due to its efficacy in controlling biofilm growth, and that is why it may be considered useful in the treatment of biofilm on intraperitoneal catheters.

We report here the clinical case of a 61-year-old man who had been diagnosed with advanced chronic kidney disease (CKD) secondary to diabetic nephropathy since 2001. He started PD in December 2006. The patient has had three episodes of peritonitis since February 2008 that led us to consider removing the catheter in October 2009 due to suspected biofilm.

In May 2010 he had a new episode of peritonitis and was started on intraperitoneal empiric treatment with vancomycin following normal dosage guidelines (a shock dosage of 2g followed by 2g/3 days and a shock dosage of 100mg of tobramycin and 50mg/24h). The presence of *Staphylococcus epidermidis* and *Streptococcus viridans* which were only sensitive to carbapenems was found four days later when the culture results were received. We, therefore, continued with the intraperitoneal treatment with vancomycin at a dose of 2g a week (3 weeks), and tobramycin was changed for 1g of imipenem/24h for 14 days.

He had a new relapse in June 2010 and *S. epidermidis* with intermediate sensitivity to vancomycin (MIC=2) was isolated. Treatment with vancomycin was started according to protocol, with a positive clinical response, although after this relapse, it was suspected that the peritoneal catheter had been colonised by *S. epidermidis* biofilm. An application was made for the compassionate use of intraperitoneal daptomycin on the basis of the previous experience of two clinical cases published. Treatment with vancomycin was maintained until daptomycin was authorised.

We used the following treatment plan with daptomycin:

A shock dosage of 200mg (in a 2l PD1 solution), followed by 40mg in each change of the intraperitoneal fluid (four times a day) for 10 days. After finishing this treatment plan, the catheter was then put in an antibiotic lock with 350mg in 7ml for 12h once a week for one month. The patient responded positively to this treatment and has had no relapses or new episodes of peritonitis.

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L. García-López[1], L. Gómez Sayago[1], M.J. Fernández-Reyes Luis[2]
[1] Pharmacy Department.
General Hospital of Segovia, Spain
[2] Nephrology Department.
General Hospital of Segovia, Spain
Correspondence: L. García-López
Servicio de Farmacia.
Hospital General de Segovia.

Relapses in patients with microscopic polyangiitis with persistently positive antimyeloperoxidase for 4 years using maintenance immunosuppressants

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To the Editor,

Anti-neutrophil cytoplasmic antibodies (ANCA) are antibodies directed against neutrophil granulocytes and monocytes.[1] These ANCA are essential markers and help to classify small-vessel vasculitides, such as Wegener's granulomatosis (WG), microscopic polyangiitis (MP) and renal-limited vasculitides, which are classified as ANCA-associated systemic vasculitides.[2]

The diagnosis can be confirmed when ANCA are detected. This means that treatment with steroids and immunosuppressants can be started without delay.[3] In contrast to anti-glomerular basement membrane antibody (anti-GBM) disease, these vasculitides are chronic diseases with a high relapse rate which leads to increased morbidity/mortality.[4] Thus, a diagnosis of relapse in a patient with ANCA-associated small-vessel vasculitis with persistently negative ANCA titre at the moment of a possible relapse should be questioned, requiring either histological proof of disease activity or exclusion of other diagnoses.[5] On the other hand, whether persistently positive levels of ANCA or an increase in their levels can predict vasculitis disease activity is more controversial.[4,5]

We describe here the case of a patient diagnosed with MP with positive ANCA at the time of diagnosis. The patient did not have any relapses for 7 years while the ANCA were negative and then had 2 relapses in the following 4 years with persistently positive ANCA and while under immunosuppressive maintenance therapy.

The patient was a 74-year-old male diagnosed with ANCA-positive MP (anti-myeloperoxidase [anti-MPO] antibodies at a titre of 320U/ml, negative anti-PR3 antibodies) in September 1999. He was treated with oral prednisone at 1mg/kg and monthly pulses of 750mg of cyclophosphamide for 6 months. He also had a medical history of tuberculosis in his youth; spondyloarthrosis and osteoporosis; collapse at D10 vertebra as a complication of steroid treatment; chronic hepatitis with positive HBs-Ag, and positive anti-HBe coinciding with the diagnosis of vasculitis. The patient had been asymptomatic for 7 years with stable kidney function (oscillations of serum creatinine with a range of 1.3-1.8mg/dl), persistently negative ANCA and without immunosuppressive maintenance therapy. From the seventh year following diagnosis of MP, we started to detect positive ANCA (positive anti-MPO). The follow-up of the evolution of the ANCA, kidney function parameters and the immunosuppressive treatment established is shown in Table 1.

A year and an half after detecting the positive ANCA, the patient was admitted for a respiratory infection without pulmonary consolidation which was treated with levofloxacin. During this hospitalisation, plasma creatinine was 1.4mg/dl, proteinuria 0.28g/24h, C-reactive protein 13mg/dl and an ANCA titre that oscillated between 410 and 429U/ml was found.

The first relapse of the disease was found two years and 3 months after the ANCA had become positive and while the patient was undergoing immunosuppressive treatment with oral cyclophosphamide at 50mg/day. The patient had anti-MPO at a titre of 367U/ml and the relapse appeared as acute non-oliguric renal failure (creatinine peak at a maximum of 6.6mg/dl), microscopic haematuria and pulmonary haemorrhage in the right lung (Figure 1) that responded to treatment with 500mg pulses of 6-methylprednisone i.v. (three doses) followed by oral prednisone at 1mg/kg/day and 500g pulses of cyclophosphamide. Two months after this first relapse, the patient was admitted to hospital for another respiratory infection without pulmonary consolidation that responded well to levofloxacin.

The second relapse of the disease was detected four years after the reappearance of the ANCA. This was also seen in the deterioration of kidney function (serum creatinine peak at 4.1mg/dl) and microscopic haematuria and with anti-MPO titres of 126U/ml. The patient responded well to treatment with 500mg pulses of 6-methylprednisolone followed by a descending dosage of oral prednisone starting at 1mg/kg/day and treatment with mycophenolate mofetil at a dose of 500mg/day. The patient was asymptomatic three months after this second relapse with a serum creatinine level of 2.7mg/dl, persistent microhaematuria (20-25 red blood cells/field), a C-reactive protein of 0.7mg/dl and an anti-MPO titre of 13U/ml.

Relapses are the main problem of vasculitides given that they cause mortality and morbidity to increase: chronic organ damage (renal failure) and increased cumulative immunosuppressive therapy toxicity.[4,6] Although the value of ANCA is well established in the diagnosis of these diseases, the usefulness of measuring ANCA titres in assessing disease activity is more controversial.[7] Increased anti-PR3 is associated with a relapse in patients with WG, whereas,