Abstract

Cyclophosphamide (CYC) is a classical drug for the treatment of severe Wegener’s granulomatosis (WG). However, as it causes substantial toxicity, alternative agents should be considered if optimal therapeutic CYC dose is not tolerated by an individual patient. We report the successful use of mycophenolate mofetil (MMF) in a 35-year-old patient with renal biopsy-proven pANCA WG and lung involvement. Despite a good clinical and biological response to the standard induction of remission therapy, the patient developed persistent severe CYC-related leucopenia after two months of treatment. Thus, CYC was replaced by MMF, and during the three and a half years of follow-up the patient never required haemodialysis. He has remained in complete clinical remission for the last two years, without MMF-related adverse effects.

Keywords: Wegener’s Granulomatosis; Cyclophosphamide; Mycophenolate Mofetil.

Introduction

Wegener’s granulomatosis (WG) is a systemic necrotizing vasculitis of small and medium size vessels, classically involving the respiratory tract and the kidneys. The presence of pathogenic serum ANCA and a biopsy of the affected organ helps for diagnostic confirmation. Cyclophosphamide (CYC) increased dramatically the long-term survival rates of WG patients, however its toxicity is substantial and therefore other agents should be used when CYC is not tolerated. Recently, Mycophenolate mofetil (MMF) has been used as a possible alternative for induction of remission and maintenance treatment. We describe a newly diagnosed WG young patient with a follow-up of three and a half years, successfully managed with MMF.

Case Report

A 35-year-old male, construction worker, with a month history of hypertension, hematuria, and impaired renal function, presented to the emergency department complaining of dyspnea, hemoptysis and chest pain. His blood pressure was 149/84 mmHg, heart rate 112 bpm, respiratory rate 42 cpm and temperature 37.6°C. Pulmonary examination revealed bilateral crepitations. The otorhinolaryngology evaluation showed bleeding from the pos-
terior pharynx.

At admission he presented anemia (Hb 6.2 g/dL), with normal leukocyte and platelet count, an elevated erythrocyte sedimentation rate (ESR) of 112 mm/h (normal range <10.0 mm/h) and C-reactive protein (CRP) concentration of 15.3 mg/dL (normal range < 0.50 mg/dL). Coagulation was normal. The blood level of urea nitrogen (BUN) was 117 mg/dL (normal range 14-42 mg/dL) and serum creatinine 2.9 mg/dL (normal range 0.6-1.3 mg/dL). Lactate dehydrogenase (LDH) was 1355 U/L (normal range 200-480 U/L). The arterial blood gas (ABG) revealed hipoxemia. Urine test strip (Combur test®) contained 3+ protein, 3+ blood, and 2+ leukocytes. The chest radiograph showed bilateral alveolar infiltrates (Figure 1A).

He was transferred to the Intensive Care Unit (ICU) for ventilatory support with the clinical suspicion of lung-kidney syndrome and treated with intravenous antibiotics and corticosteroids because of severe respiratory failure, with symptomatic improvement.

Antinuclear antibodies (ANA), extractable nuclear antigen (ENA) and antiglomerular basement membrane antibodies (anti-GBM) tests were negative. Indirect immunofluorescent test for antineutrophil cytoplasmic antibodies (ANCA) was positive, giving a perinuclear staining (pANCA), and was confirmed by enzyme-linked immunosorbent assay (ELISA) as anti-myeloperoxidase (anti-MPO) positive (anti-proteinase 3 negative). The adenosine desaminase (ADA) and angiotensin-converting enzyme (ACE) levels were normal. The screening for an infection was negative.

The urinalysis study revealed proteinuria of 7.4 g/24h (normal range 0.05-0.08 g/24h) and a creatinine clearance of 39.2 ml/1.73 m² (normal range 90-139 ml/m²). The urinary sediment evidenced blood, proteins, leukocytes and no red cell (RBC) casts. The thoracic CT scan showed extensive bilateral diffuse alveolar infiltrates suggestive of diffuse alveolar hemorrhage (DAH) (Figure 1B).

WG was diagnosed and treatment with intravenous methylprednisolone daily pulses (MTP-p) of 1g for 3 days, followed by daily oral corticosteroids (OCS) prednisolone (1mg/kg · 60 mg) and oral CYC (100 mg) started. Trimethoprim-sulfamethoxazole (TMP/SMZ 160/800 mg) three times a week for Pneumocystis jiroveci pneumonia prophylaxis was added. After clinical improvement, a renal biopsy was performed, evidencing a diffuse endo-extra-capillary pauci-immune proliferative glomerulonephritis in an advanced sclerosing stage with intense chronic interstitial nephritis and granuloma (Figure 2).

The evolution was markedly favourable (see Figure 3 for details). Two weeks after initiation of treatment with CYC, serum creatinine decreased to 1.5 mg/dL and CRP normalized (0.5 mg/dL). The BVAS/WG, a validated disease-specific activity score, which captures all possible organ manifestations of the disease, fell from 13 at presentation to 3. The patient was discharged in a stable condition.

After two months of CYC, he developed severe leucopenia (0.9x10⁹/L), which did not resolve after dosage reduction. The patient was re-hospitalized, treated with granulocyte colony-stimulating factor (G-CSF) and CYC was discontinued. Several days later, due to gastrointestinal bleeding, a colonoscopy with biopsy was performed revealing a tubulovillous adenoma with high-grade dysplasia which was resected. Oral corticosteroids were maintained.

Three and a half months later, the CRP had normalized (0.2 mg/dL) and the ESR had decreased to 32 mm/h. Proteinuria (6.1 g/day) and active urinary sediment persisted; serum creatinine remained stable at the baseline value of 2.0 mg/dL, while the pANCA elevated titres persisted (31 U). Mycophenolate mofetil was instituted at an initial dose of 1g/day. At this moment, the leukocyte count was normal. Seven weeks later, the patient developed dyspnea with respiratory insufficiency and bilateral pulmonary infiltrates, without renal function deterioration (serum creatinine 1.8 mg/dL; proteinuria 2.5 g/day with active urinary sediment). Both acute phase parameters were elevated (CRP 12.5 mg/dL; ESR 86 mm/h); the pANCA titer was 29.7 U. These features were consistent with a recurrence of pulmonary vasculitis that resolved with MTP-p of 1g for 3 days followed by prednisolone 60 mg/day and an increase of MMF dose (1.5 g/day). The BVAS/WG score was 5.

After three months, the respiratory insufficiency recurred with constitutional features. Chest radiograph disclosed moderate infiltrates. The ESR was 75 mm/h and the CRP was 2.3 mg/dL. The creatinine level rose again to 2.9 mg/dL and pANCA titer was 33 U. A screening for an infection was negative. The BVAS/WG score was 5. A new course of MTP-p followed by OCS was administrated and the MMF dosage was further increased to 2 g/day with clinical improvement. One month later, the
patient was asymptomatic. A value of 1 was recorded for the BVAS/WG score; however, he had developed corticosteroid-induced diabetes mellitus and premature cataract. OCS were tapered down while he was maintained on MMF 2g/day and TMP/SMZ prophylaxis.

Three months later, the patient had a cutaneous infection due to Staphylococcus hominis that was rapidly controlled with antibiotics. Since then the patient initiated a sustained complete clinical remission with no signs or symptoms suggestive of active vasculitis (BVAS/WG=0). Six months later, the OCS were discontinued and the patient was maintained on MMF 2g/day and TMP/SMZ prophylaxis. Seven months later, the patient started a gradual MMF tapering, being its dosage 500 mg/day after six months.

The clinical course of the patient, the therapy as well as some objective parameters that were monitored on follow-up are illustrated in Figure 3.

Discussion

Before CYC, patients with severe WG had a mortality rate of 80% within the first year after the diagnosis. The combined treatment with corticosteroids resulted in marked improvement or partial remission (PR) in 91% of patients and complete remission (CR) in 75% of patients. Unfortunately, CYC exposes patients to severe life-threatening side-effects. MMF is an immunosuppressive drug used in

Figure 1. Chest imaging at hospital admission showing extensive diffuse bilateral alveolar infiltrates. A. Chest X-ray. B. Thoracic CT scan.

Figure 2. Renal biopsy A. Diffuse endo-extracapillary proliferative glomerulonephritis (H/E x400). B. Specimen showing ischemia and granuloma (MAR x400).
transplant medicine with rather low toxicity due to its lymphocyte-selective mode of action and therefore representing an attractive drug for the treatment of autoimmune disorders with pathogenic autoantibodies, such as ANCA-associated small vessel vasculitis (AASVV).

A 52-weeks pilot study assessed the effectiveness of MMF in inducing remission in subjects resistant to CYC. Twelve AASVV subjects were enrolled, including 7 with WG (3 CYC-resistant and 4 with relapses). The response to MMF varied in the study group. Although transient CR and favourable long-term response could be induced in 6 of 10 evaluable subjects, only a minority (n=3) achieved a long-lasting remission. Another study addressed the efficacy of MMF as alternative to CYC for induction of remission in 32 patients with active AASVV (29 WG and 3 MPA) who could not be treated with CYC (all except 1 patient had already been treated for previous relapse episodes). CR was achieved in 25 patients (78%), PR in 6 (19%) after 2.2 (1-5) months, whereas 1 (3%) patient did not respond. Nineteen patients with initial response relapsed 12 (2-58) months after starting the treatment. The median relapse-free survival on MMF therapy was 16 months, which is comparable to the interval between the previous relapse and the current treated episode of active disease (17 months).

On the other hand, two small trials examined the safety of MMF for maintenance therapy in patients with active WG after achieving remission with CYC and glucocorticoids. In a 50-month study, all the enrolled patients (n=14) had WG, of these, 5 were in the initial phase of their disease and 9 experienced a relapse. Although MMF effectively maintained remission in 8 patients for a median time of 27 months, disease relapse occurred in 6 with a median time from remission to relapse of 10 months (range 1-25 months). The relapse rate was (6/14; 43%). In another 15-month study, only 1 WG out of 11 patients recruited (2 patients with MPA and 9 with WG), relapsed at the 14th month of maintenance therapy, what gives a WG-specific relapse rate of (1/9;11%). It is worth noting that the authors of this study, successfully prescribed MMF as an induction treatment to replace CYC at week 9 in an intolerant-to-CYC MPA patient.

In the case reported, agents other than MMF were considered as rescue therapy to resume the treatment after the prematurely withdrawal of CYC therapy. One of them, methotrexate (MTX), is con-
Cyclosporine (CYC) is indicated in patients with renal insufficiency\(^6\), being effective, from the time of diagnosis, only for less severe forms of the disease.\(^10\) Azathioprine (AZA) can be used in the setting of renal insufficiency, however, it has not been found to effectively induce remission of active major organ disease.\(^7\) Biologic therapies, that target specific immunologic components involved in the pathogenesis of WG disease are being explored, and constitute new options beyond steroids and cytotoxic drugs.\(^11\) Our choice was dictated by MMF safety profile, case series reports and our own previous satisfactory experience with this drug in other diseases including lupus nephritis (LN).

Besides the more conventional adverse effects of MMF derived from its use in the setting of WG\(^4\)-\(^7\), a hitherto unknown side effect of this drug has been recently reported.\(^12\) According to this report, the administration of MMF at a dose of 2 g/day in two longstanding relapsing WG patients, caused a severe acute inflammatory syndrome characterized by fever, arthralgias and severe muscle pain, that necessitated interruption of the therapy. This reaction was attributable to the systemic proinflammatory cytokine release, induced by one of its metabolites.

In conclusion, the treatment with MMF was effective and well tolerated. The therapy with MMF was able to reduce to maintain the disease activity at zero. However, to date, there is still not enough published evidence to support the use of MMF in patients with active WG on a large scale. No randomized studies comparing the efficacy of MMF with CYC administered from the diagnosis have been undertaken in AASVV in general and WG in particular. We report on the effective use of this drug in a WG patient who was intolerant to CYC in the acute phase of the disease. In this regard, we advocate an individualized treatment.

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