

# Combination of Steroids and Azathioprine in the Treatment of Ormond's Disease – A Single Centre Retrospective Analysis

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**Abstract:** We present a retrospective analysis of patients treated in our Department of Clinical Biochemistry, Haematology and Immunology, Na Homolce Hospital, during 1997–2013 for Ormond's disease. We analyse the clinical history, diagnostic approaches, surgical, and immunosuppressive therapies and their subsequent effect on our patients. 28 patients treated for Ormond's disease were included. Patients with established disease activity (26 patients) were given immunosuppressive treatment, using corticosteroids in combination with azathioprine. Treatment response was evaluated using clinical symptomatology, inflammatory parameters and imaging methods. In the cohort as a whole, immunosuppressive therapy was applied in 26 patients; in two patients it was not used as no inflammatory activity was found with the disease. In all 26 patients, computed tomography showed that immunosuppressive treatment resulted in partial or complete regression of inflammatory infiltrate. Out of the total number of 26 patients, two patients experienced disease exacerbation 7 and 16 months after the immunosuppressive treatment was discontinued. The longest follow-up period was 16 years; the shortest one was 21 months. Idiopathic retroperitoneal

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fibrosis – Ormond’s disease – is a disease with serious complications. Standard treatment involves a combination of surgery and immunosuppressive treatment. The combination of corticosteroids and azathioprine represents a potentially safe and useful method of treatment.

## Introduction

Ormond’s disease – idiopathic retroperitoneal fibrosis – is a relatively rare disease with an unclear aetiology, characterised by chronic periaortitis and retroperitoneal fibrosis (RF). The inflammatory process affects the infrarenal part of the abdominal aorta and the iliac arteries, and the presence of infiltrates encasing the ureters and inferior vena cava is also commonly found. Its incidence is 1.3 in 100,000 people (van Bommel et al., 2009). This disease is currently classed as an immunoglobulin G4-related disease. The course of the disease is associated with the incidence of complications, the most serious of which are renal failure and aneurysm of the abdominal aorta or the iliac arteries. Thanks to advances in medicine, diagnostic and, in particular, therapeutic strategies are gradually changing. Improved results from pharmacotherapeutic regimens have led to a greater emphasis on early comprehensive medication therapy with corticosteroids and new immunosuppressive or immunomodulatory drugs. In our retrospective survey, we describe the clinical history, diagnostic approaches, surgical, and immunosuppressive therapies and their subsequent effect on our patients.

## Patients and Methods

### *Patients and setting*

Between 1997 and 2013 our Department of Clinical Biochemistry, Haematology and Immunology, Na Homolce Hospital, in collaboration with Department of Urology and Department of Vascular Surgery, diagnosed and subsequently treated 28 patients with idiopathic RF. The demographic data for these patients are shown in Table 1. The disease was diagnosed on the basis of a comprehensive clinical examination, using biochemical, immunological, and microbiological tests, and imaging methods including ultrasound, computed tomography (CT), positron emission tomography/computed tomography (PET/CT), and CT/arteriography. Clinical symptoms at onset were back pain, flank pain, fatigue, weight loss, fever,

**Table 1 – Patient demographics and laboratory characteristics**

	N	Age	CRP mg/l median	ANA positive	anti dsDNA	Rheumatoid factor	Autoimmune disease
Male	16	56.8	38.2	6 (31%)	negative	negative	1
Female	12	51.4	41.7	4 (28%)	negative	negative	7

CRP – C-reactive protein; ANA – antinuclear antibodies; dsDNA – double stranded deoxyribonucleic acid

and night sweats. Laboratory screening included a biochemistry panel, screening for hepatitis B and C, serum levels of immunoglobulin G (IgG) and the subclasses IgG1–IgG4, and the erythrocyte sedimentation rate (ESR). Patients were also examined for the presence of antinuclear antibodies, extractable nuclear antibodies, and antibodies to double-stranded DNA. RF was considered if soft-tissue density surrounded the infrarenal aorta or iliac vessels on contrast-enhanced CT and/or on histologic confirmation. Disease activity was confirmed by a PET/CT scan in 21 patients upon the initiation and discontinuation of immunosuppressive therapy. In eight patients, a biopsy sampling collection was performed percutaneously using a biopsy needle under CT navigation, whereas in one patient, laparoscopy was used to collect the sample. The diagnosis of Ormond's disease was confirmed in all the biopsied samples by subsequent histological examination. The examinations into the presence of IgG4 producing plasma cells, performed in a small number of patients (three) are not reported.

#### *Treatment*

Patients with established disease activity (26 patients) were given immunosuppressive treatment, using corticosteroids in combination with azathioprine. The initial dose of prednisone was 0.75–1 mg/kg and that of azathioprine was 2×50 mg/day. After systemic symptoms were resolved and the inflammatory markers reached negative values, corticosteroids were reduced as follows: prednisone by 10 mg a month to reach a daily dose of 10 mg; azathioprine was administered in the dose of 2×50 mg for six months and then discontinued. A follow-up CT or PET/CT scan was performed after six months of treatment. In the absence of inflammatory activity, i.e. negative biochemical parameters and a negative PET/CT scan, prednisone treatment was reduced to 5 mg/day and discontinued after two months. Where indicated, surgical procedures were applied, including ureteral stenting, nephrostomy, stenting of arteries, or arterial aneurysm surgery.

#### *Outcomes and follow-up*

The primary outcome was the reduction of clinical symptoms, extubation of obstructed ureters, and reduction of soft tissue mass, followed by the absence of inflammatory activity on a PET/CT scan. The secondary end-points included monitoring of the biochemical parameters of renal function, IgG4 concentration, and reaching normal values of inflammatory biomarkers. The patients were monitored at regular intervals of four to six weeks in the first three months when biochemical and immunological parameters were monitored. After inflammatory markers became insignificant, this interval was extended to two months. Follow-up CT or PET/CT scans were performed after the first six months and after a further three to six months in patients requiring longer treatment. The longest follow-up period was 16 years; the shortest one was 21 months.

## Results

Table 1 shows the patient laboratory and demographic characteristics. Eighteen patients presented with clinical symptoms of ureteric obstruction with hydronephrosis, renal insufficiency (two patients) or renal failure (one patient). Ten cases involved patients with periaortitis, with aneurysms of the aorta and/or iliac arteries present in five of these. After laboratory testing, ten patients were found to be positive for antinuclear antibodies, without evidence of specificity for extractable nuclear antibodies. None of the patients tested positive for antibodies to double-stranded DNA. Other autoimmune diseases were present in eight patients, in which seven cases were identified as autoimmune thyroiditis and one case as Sjögren's syndrome. IgG4 concentrations were examined in 18 patients. In eight patients, an increased IgG4 concentration was found. The IgG4 concentration was within the normal range in all patients after immunosuppressive therapy. Hydronephrosis was found in 18 patients; 10 patients showed impairment of one ureter and 13 patients had impairment of both ureters. In two patients, despite an initial diagnosis of renal insufficiency, subsequent surgical intervention and immunosuppressive therapy resulted in the recovery of renal function. The standard surgical solution involved the insertion of stents, and a nephrostomy was performed on one patient. In all 26 patients, CT showed that immunosuppressive treatment resulted in partial or complete regression of the inflammatory infiltrate. After termination of the immunosuppressive therapy, 32 (89%) of the 36 ureters were successfully extubated. The presence of an abdominal aortic aneurysm was found in five patients and iliac artery aneurysms in two patients. Surgical treatment was indicated for aneurysms in four cases prior to the deployment of immunosuppressive therapy. In the case of one patient with an aneurysm, surgical treatment was not indicated after the initial diagnosis, but four months after the termination of immunosuppressive treatment, the size of the aneurysm was found to have increased and required surgery. Four patients who underwent surgery for aneurysms were subsequently given standard immunosuppressive treatment, with no exacerbation of the disease for six months after its termination. In the cohort as a whole, immunosuppressive therapy was applied in 26 patients; in two patients, it was not used as no inflammatory activity was found with the disease. In all 26 patients, a combination of corticosteroids and azathioprine was used. Out of the 26 patients, two patients experienced disease exacerbation 7 and 16 months, respectively, after immunosuppressive treatment was discontinued. The longest follow-up period was 16 years; the shortest one was 21 months. Out of the total number of 28 patients, 25 are still alive. One patient died of an acute abdominal event, and two patients died of cancer 35 and 17 months, respectively, after the discontinuation of immunosuppressive therapy.

## Discussion

Idiopathic RF is a systemic disease of as yet unexplained pathogenesis. The term covers a number of common diseases – chronic periaortitis, inflammatory abdominal aortic aneurysm and perianeurysmal RF. Approximately two-thirds of RF cases are idiopathic, i.e. no primary specific cause has been identified. In this case, the condition is known as Ormond's disease. In one-third of patients, symptoms of fibrosis are found after primary malignancy, infection, or iatrogenic effects of medication (Vaglio et al., 2006). In 70% of patients, the first symptoms of the disease are recorded between 30 and 60 years of age; in idiopathic RF, men predominate in a ratio of 2:1. In typical cases where RF manifests, confirmation of the diagnosis is based on the medical history, clinical findings, and imaging results (Restrepo et al., 2011; Schmidt, 2013). Ormond's disease is a condition currently classified as an IgG4-related disease (Zen et al., 2012; Brito-Zerón et al., 2014). These disorders are characterised by increased concentrations of IgG4 in the serum and the presence of IgG4-producing plasma cells in the infiltrate. The pathognomonic significance of the antibodies produced has not yet been sufficiently determined. Published studies suggest that only a portion of patients with Ormond's disease meet this criterion (Zen et al., 2009; Takahashi et al., 2010; Laco et al., 2013). In our cohort, we found increased concentrations of IgG4 in the serum in eight patients, whereas measurements were taken from 18 patients before starting immunotherapy. Findings of elevated levels of IgG4 in the serum had no effect on the success of immunosuppressive therapy. Clinical disease presentation did not vary among patients with increased or normal IgG4 concentration. In the context of these results and in line with results from other studies (Koo et al., 2015), it would appear that not all patients with RF fall into the category of IgG4-related disease. After successful immunosuppressive therapy and remission, we found that the concentrations of IgG4 in the serum of all patients who had previously shown elevated levels had normalised. One of the complex and very important issues to be addressed in the diagnosis of RF involves distinguishing between an infectious and non-infectious aetiology of the inflammation. The emergence of a retroperitoneal or para-aortal infiltrate may also be induced by an infectious aetiology. Given the use of immunosuppressive therapy, failure to recognise this difference may have fatal consequences for the patient. Potential causative agents may include viruses (hepatitis), mycobacteria, and bacteria, i.e. *Staphylococcus aureus*, *Salmonella*, etc. (Cartery et al., 2011). In our group, we performed biopsy investigations under CT in eight cases; in one patient, we removed a biopsy specimen laparoscopically as it was not possible to remove it using a thin needle under CT. This was a patient with a suspected infectious aetiology (tuberculosis, TB) with a positive test for interferon gamma production and indications of this aetiology from the PET/CT image. Although an examination of the biopsy sample using molecular biological methods failed to confirm TB, this patient underwent anti-TB treatment along with immunosuppressive therapy. Given

the typical clinical findings, including the results of imaging methods, no biopsies were carried out on the other patients.

It is noteworthy that not all patients demonstrate disease activity using standard inflammatory markers (ESR, C-reactive protein). Here, our results are in agreement with the study by Pelkmans et al. (2012), where the negativity or positivity of acute phase reactants did not affect the final clinical outcome of patients after treatment. In our group, there were two patients for whom ESR and C-reactive protein were negative in the initial tests. Subsequent PET/CT examinations failed to find inflammatory activity in these patients. In the two patients with negative PET/CT results, we did not initiate immunosuppressive treatment, and they were routinely monitored. They currently show no increase in inflammatory activity after 2 and 3 years of follow-up, respectively. We believe that the disease can also be diagnosed in its chronic phase, when inflammatory activity may disappear spontaneously. The most valuable indication of disease activity is the PET/CT examination, which we use for each patient before deploying immunosuppressive treatment, as well as when deciding to terminate it. In this respect, it would be advantageous to find new biomarkers which could indicate the activity of the disease with a lower cost and burden placed on the patient compared with PET/CT. An example of this type of marker could be pentraxin 3 (Dagna et al., 2011).

For our patients, we used an initial dose of 0.75–1 mg of prednisone per kilogram of body weight, gradually reducing this over a treatment period of six months. After this period, we carried out PET/CT monitoring and, depending on the results, decided whether or not to extend the treatment. The maximum period of treatment was 24 months, with 5 mg/day doses of prednisone maintained over that time. Before administering azathioprin, we always carried out a pharmacogenomic assessment using thiopurine S-methyltransferase, which identified any high-risk patients (Ford and Berg, 2010).

We diagnosed our first patient with RF in 1997, and this patient has also undergone the longest follow-up period – 16 years. Of 28 patients, three died; in one case the cause was an acute abdominal disorder, with no apparent link to Ormond's disease, and two cases were due to cancer which occurred two and three years, respectively, after the termination of immunosuppressive treatment. In addition to the treatment methods referred to above, cyclophosphamide, cyclosporine A and tamoxifen are also used to treat patients with RF (Marzano et al., 2001; Binder et al., 2012; Brandt et al., 2014). Mycophenolate mofetil appears promising given its antifibrotic effects (Scheel et al., 2011). An alternative treatment for patients who do not respond adequately to treatment with corticosteroids, or for whom this therapy is associated with a higher risk, involves biological disease modifiers. These include tocilizumab, an antibody against the interleukin-6 receptor, or rituximab, a monoclonal antibody against CD20 (Maritati et al., 2012; Vaglio et al., 2013).

There are several limitations to our study: the small number of patients, the retrospective nature of the evaluation, and the absence of histopathological assessments detecting IgG4 plasma cells in the infiltrate. On the other hand, we could not find any study in the literature with this many patients treated with a combination of corticosteroids and azathioprine.

## Conclusion

Idiopathic RF – Ormond’s disease – is a disease with serious complications including renal insufficiency or failure and aneurysm of the abdominal aorta or iliac arteries. Its diagnosis is based on an exact diagnosis from a biopsy, or a combination of imaging methods and immunological, biochemical, and microbiological tests. Standard treatment involves a combination of surgery and immunosuppressive treatment and, provided it is applied in a timely manner, patients can expect a favourable clinical outcome.

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