

UNIVERSITA' DEGLI STUDI DI PARMA

Dottorato di Ricerca in Fisiopatologia dell'Insufficienza Renale

Ciclo XXI

**TRIAL RANDOMIZZATO DI CONFRONTO TRA PREDNISONA E
TAMOXIFEN NEL TRATTAMENTO DELLA FIBROSI
RETROPERITONEALE IDIOPATICA**

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Riassunto

Background e scopi dello studio. La fibrosi retroperitoneale idiopatica (FRI) è una malattia rara il cui trattamento è ancora empirico data l'assenza di trial randomizzati controllati. I corticosteroidi sono i farmaci più utilizzati, ma recenti reports hanno mostrato l'efficacia del tamoxifen. Scopo di questo studio è confrontare l'efficacia di prednisone e tamoxifen nell'indurre una remissione clinica in pazienti con FRI.

Metodi. I pazienti con interessamento ureterale venivano sottoposti a decompressione ureterale (stent, nefrostomia, ureterolisi chirurgica) prima dell'ingresso in studio. Tutti i pazienti ricevevano prednisone 1 mg/kg/die per 1 mese, al termine del quale, se avevano ottenuto una "risposta iniziale" (remissione dei sintomi e normalizzazione degli indici di flogosi), venivano randomizzati per tamoxifen (0.5 mg/kg/die per 8 mesi) o prednisone (0.5 mg/kg/die a scalare per 8 mesi). L'end-point primario dello studio era il raggiungimento della remissione completa, definita come assenza di complicanze ostruttive ureterali in assenza di stent o nefrostomie, assenza di sintomi e normalizzazione degli indici di flogosi.

Risultati. Venivano arruolati 40 pazienti con FRI; di questi, uno veniva escluso dopo revisione della diagnosi, e tre presentavano tossicità acuta da steroide durante il I mese di terapia; i restanti 36 ottenevano una "risposta iniziale" al termine del I mese e venivano quindi randomizzati per prednisone (n=18) o tamoxifen (n=18). Al termine degli 8 mesi di terapia, 17 (94.4%) dei pazienti trattati con prednisone ed 11 (61.1%) dei pazienti trattati con tamoxifen erano in uno stato di remissione clinica (p=0.04). I pazienti trattati con prednisone mostravano anche una più marcata riduzione dello spessore della FRI (p=0.05 a livello peri-aortico e p=0.02 a livello peri-iliaco). Tre dei pazienti che avevano raggiunto la remissione nel braccio tamoxifen (27.3%) e 4 dei pazienti che avevano raggiunto la remissione nel braccio prednisone (23.5%) presentavano recidive post-trattamento (p non significativa).

Considerando le recidive occorse sia durante che dopo il trattamento, il tempo intercorso tra la remissione e la recidiva era tendenzialmente più lungo nei pazienti trattati con prednisone rispetto al braccio tamoxifen ($p=0.19$).

Conclusioni. Il prednisone è significativamente più efficace del tamoxifen nell'indurre remissione di malattia in pazienti con FRI.

Introduction

Retroperitoneal fibrosis is a rare condition, characterized by the presence of a retroperitoneal fibro-inflammatory tissue which usually develops around the abdominal aorta and the iliac arteries and envelops surrounding structures such as the ureters, the inferior vena cava, the mesenteric arteries and the duodenum (1, 2). Retroperitoneal fibrosis is idiopathic in most cases (idiopathic retroperitoneal fibrosis, IRF), but it can also be secondary to a variety of etiologies, such as tumours (primary retroperitoneal or metastatic retroperitoneal neoplasms), infections (e.g. tuberculosis), major abdominal surgery, radiation therapy, use of drugs (e.g. ergot derivatives, pergolide, methysergide), systemic diseases (e.g. amyloidosis), and the non-Langerhans cell histiocytosis Erdheim-Chester disease (3, 4). IRF may be limited to the retroperitoneum or arise in the setting of a systemic sclerosing disorder also affecting other sites such as the mediastinum (mediastinal fibrosis), the pancreas (sclerosing “autoimmune” pancreatitis), the liver (sclerosing cholangitis), and the salivary glands (chronic sclerosing sialoadenitis). Moreover, IRF may also be associated with systemic autoimmune or inflammatory diseases, such as systemic vasculitis (5), rheumatoid arthritis (6), psoriasis (7), and autoimmune thyroiditis (8).

IRF is histologically characterized by marked fibrosis and a chronic inflammatory infiltrate composed of lymphocytes, plasma cells, macrophages and eosinophils. This fibro-inflammatory reaction extends from the adventitia of the abdominal aorta and the iliac arteries into the retroperitoneum. IRF may develop around an undilated aorta or around an aneurysmal aorta: the latter form is also known as perianeurysmal retroperitoneal fibrosis or inflammatory abdominal aortic aneurysm. All of these forms have common histopathological features and overlapping clinical manifestations and are therefore included into the clinico-pathological entity referred to as “chronic periaortitis” (4, 9, 10).

The clinical presentation of IRF is characterized by the frequent presence of constitutional symptoms (e.g. fatigue, anorexia, weight loss, low-grade fever) and back or abdominal pain, which may be dull and persistent or also colic-like, particularly when IRF causes severe ureteral obstruction (11-13). Less common (but still relatively frequent) manifestations include testicular pain, hydrocele, varicocele, lower extremity edema, constipation, deep vein thrombosis of the lower limbs, or severe hypertension due to renal artery involvement by the retroperitoneal mass (11, 13, 14). Ureteral involvement is the most frequent complication of IRF; in some patients, the ureters may only show medial deviation, but in the majority of patients unilateral or bilateral ureteral obstruction occurs. Bilateral involvement may be synchronous or metachronous and often causes acute renal failure. Conversely, chronic renal insufficiency is rare. Notably, some patients show at presentation an atrophic kidney, presumably the result of long-standing, silent ureteral entrapment.

The treatment of IRF should aim at relieving ureteral obstruction or other disease-related complications, and then switch off the systemic inflammatory reaction. The relief of obstruction can be achieved by means of surgical ureterolysis or “conservative” techniques such as placement of ureteral stents or nephrostomy tubes. Medical therapy is usually instituted once the obstruction has been resolved. The aims of medical therapy are to induce regression of the retroperitoneal mass, and therefore to guarantee a sustained remission of organ involvement/obstruction; in addition, medical therapy has the purpose to suppress inflammation and its related symptoms (e.g. systemic inflammatory symptoms, pain), and should be able to prevent disease relapses (2).

The medical treatment of IRF is, however, still empirical, as no prospective randomized controlled trials have been performed. Glucocorticoids are the mainstay of therapy based on observed benefit. The optimal dose and duration of steroid therapy are unclear given the

absence of large scale trials. One case series reported use of an initial prednisone dose of 60 mg every other day for two months, tapered over the subsequent few months to 5 mg daily, and continued for a total duration of therapy of two years. Nine of 11 patients who completed this regimen responded with relief of symptoms and regression of the retroperitoneal mass (15). In another study, 24 patients were treated with prednisone for one year (16); the regimen consisted of 60 mg once daily for six weeks, which was usually tapered within the following two to three months to a maintenance dose of 10 mg/day and continued for one year. If severe ureteral obstruction was present, decompression was allowed using nephrostomy tubes or in-dwelling ureteral stents. Twenty-two patients reported significant regression of symptoms and 19 had a progressive reduction in size of the retroperitoneal mass, as assessed by CT. In addition, 13 patients with initial treatment success showed disease recurrence after steroid withdrawal.

A number of small studies have also evaluated the combination of steroids and immunosuppressive drugs such as cyclophosphamide, azathioprine, and methotrexate (17-19). These regimens, although generally effective in controlling disease-related symptoms and complications, were not always safe; more importantly, it is not known whether they are more effective than corticosteroids alone.

There are an increasing number of reports using tamoxifen, principally as initial medical therapy but also as sequential treatment following steroid induction. This agent has been tried based on possible benefits observed in the treatment of desmoid tumors. Desmoid tumors and retroperitoneal fibrosis are characterized by locally invasive fibroblast proliferation, although their pathobiology, clinical and histological features differ. Positive responses to tamoxifen, used alone or in combination with corticosteroids, have been described among patients with IRF in a number of case reports (20-22). Interestingly, a

single-centre prospective study was performed using tamoxifen as the sole therapeutic agent in “non-malignant” retroperitoneal fibrosis. In this study, 19 cases of nonmalignant retroperitoneal fibrosis diagnosed by CT scan were treated with tamoxifen, and 15 had clinical improvement after only a few weeks of treatment (23). Given the good safety profile of tamoxifen, this has become a very promising therapeutic option for IRF.

In this work, we report the results of the first randomized controlled trial ever performed in patients with IRF, which compared the efficacy and safety of prednisone and tamoxifen in inducing IRF remission.

Patients and methods

Study population

We recruited all the newly diagnosed IRF patients fulfilling the study eligibility criteria seen at our department (Clinical Medicine, Nephrology and Health Sciences, University Hospital, Parma) from October 2000 through June 2006. Patients were eligible if they had a new diagnosis of IRF (either non-aneurysmal or peri-aneurysmal) and had not received any medical therapy for IRF. Patients were excluded if retroperitoneal fibrosis was secondary to other etiologies such as drugs (2), infections, cancer, radiotherapy, trauma, major surgery, Erdheim Chester disease, systemic connective tissue or vasculitic disease (e.g. SLE, panarteritis nodosa); in addition, patients were excluded if they were pregnant, had active infections or tumours, known hypersensitivity to prednisone or tamoxifen, and uncontrolled diabetes.

The diagnosis of IRF was made on the basis of abdominal contrast-enhanced CT or MRI scans, following commonly accepted criteria (2, 11, 13); retroperitoneal biopsy was required if the localization of the mass was atypical (e.g. pelvic, peri-renal, peri-pancreatic), or if there were radiological (15, 24, 25) or clinical features suggesting an underlying infection or malignancy.

If hydronephrosis was present, ureteral decompression had to be achieved prior to the start of medical therapy; any technique was allowed for relieving ureteral obstruction, i.e. ureteral stent placement via cystoscopy, percutaneous placement of nephrostomy tubes, or surgical ureterolysis.

The study was approved by the Ethics Committee of the University Hospital of Parma. All patients provided written informed consent. The study protocol was registered in *clinicaltrials.gov* (NCT00440349).

Study design and treatment protocol

This study was a phase II, open-label, single-centre, randomized controlled trial. At study entry, all patients underwent clinical examination, routine laboratory tests including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and a panel of autoantibodies, as previously described (8). Abdominal CT or MRI, chest X-ray and thyroid ultrasound were also performed at study entry.

All of the enrolled patients were treated with an induction therapy consisting of oral prednisone, 1 mg/kg/day (maximum dose 80 mg/day) for one month; calcium, vitamin D3, bisphosphonates and proton-pump inhibitors were also given. At the end of the month of induction prednisone therapy, we assessed whether the patients achieved an *initial response*. This was defined as the disappearance of disease-related symptoms (particularly pain, systemic symptoms, edema and constipation) along with normalization or near-normalization (reduction to one third of the initial value) of the acute-phase reactants ESR and CRP. The patients who obtained initial response were then randomized 1:1 to receive prednisone or tamoxifen. The patients randomized to prednisone received it at a dose of 0.5 mg/kg/day for one month, 0.25 mg/kg/day for another month, 0.125 mg/kg/day for a further two months, then the drug was tapered to zero over the ensuing four months (overall, eight months). The patients randomized to receive tamoxifen had prednisone tapered to zero within two weeks and then switched to tamoxifen, which was given at a fixed dose of 0.5 mg/kg/day (maximum, 40 mg/day) for eight months. Both prednisone and tamoxifen were withdrawn at the end of the eighth month of treatment.

Clinical and laboratory evaluations were performed on a monthly basis during treatment. Follow-up abdominal CT or MRI scans were performed at the end of the fourth month post-

randomisation and at the end of treatment (eighth month post-randomisation). Following the end of treatment, the patients were followed-up for an additional 16 months. During the post-treatment follow-up, they underwent clinical and laboratory examinations every three to six months. CT or MRI was repeated 6-8 months after the end of therapy and thereafter every year.

CT and MRI scans were assessed by two independent radiologists who were neither aware of the patients' disease course nor of their randomization arm; discrepancies in their evaluations were resolved by consensus. The modification in size of the retroperitoneal mass was assessed as follows: the maximal thickness of the mass was determined at the level of the lower abdominal aorta and the common iliac arteries at the baseline CT/MRI and at the CTs/MRIs performed at months 4 and 8 post-randomization, or at the time of a suspected disease relapse; percentage variations were then calculated.

End-points of the study

The primary end-point was the remission rate achieved by the end of treatment. *Remission* was a composite end-point, defined as the absence of disease-related symptoms (particularly pain, systemic symptoms, constipation and edema) and of hydronephrosis (assessed after removal of ureteral stents or nephrostomy tubes, if present), together with normal values of the acute-phase reactants ESR and CRP. The timing of stent or nephrostomy removal was left to the discretion of the treating clinician, and was essentially based on the clinical course of the patient, on the observation of mass shrinkage on CT or MRI, and on the presence and frequency of urinary tract infections, bleeding, or pain due to the stents/nephrostomies themselves.

Because several reports (4, 16) and our own clinical experience have shown that IRF patients may become symptom- and hydronephrosis-free even though the retroperitoneal mass does not show modification in size on CT/MRI, we did not include mass shrinkage among the criteria for defining disease remission. Similarly, as testicular complications such as hydrocele, varicocele and retrograde ejaculation usually persist despite good response to therapy, their resolution was not required for disease remission.

We considered treatment failures the following conditions: i) patients who never achieved remission (e.g., those who could never have their stents removed or never became symptom-free); ii) patients who had disease *relapses* during treatment. Relapses were defined by the presence of one or more of the following findings: reappearance of disease-related symptoms; reappearance of disease-related complications (e.g. hydronephrosis, testicular pain, leg edema); enlargement of the retroperitoneal mass on CT/MRI studies; unexplained and persistent increase in ESR and CRP levels. The choice of the optimal treatment for relapses, regardless of whether they occurred during or after treatment, was left to the treating clinician.

Secondary end-points of the study included: i) improvement in renal function, ii) reduction in size of IRF, iii) rate of post-treatment disease relapses, iv) treatment-related toxicity.

Statistical analysis

Differences in remission and relapse rates were calculated by means of Fisher's exact test. Differences in continuous variables were calculated using the Mann Whitney U test. Relapse-free survival was calculated using the Kaplan-Meier method by means of the log-rank test. All analyses were performed using the SPSS statistics software (version 17.0).

Results

Forty consecutive IRF patients (25 M and 15 F, median age 59 years, range 37-84) fulfilling the study eligibility criteria were enrolled. The diagnosis of IRF was made by means of CT in 29 patients and by MRI in the remaining 11 patients, and was histologically confirmed in 21 cases (53%). In one patient the diagnosis was revised prior to the start of therapy (tuberculosis-induced retroperitoneal fibrosis), thus she was excluded from the study; this patient was the subject of a case report (3). Thirty-nine patients started the induction therapy with prednisone. Two of them (one F and one M, respectively 82 and 75 years old) were excluded from the study because of acute steroid-related toxicity, manifesting with vertebral collapse and uncontrollable diabetes in the former and mental status changes, arrhythmias, and severe myopathy in the latter. An additional patient (M, 63 years old) refused to continue the treatment according to our prednisone schedule. Therefore, only 36 of the 40 enrolled patients (90%) completed the first month of prednisone therapy, at the end of which they all achieved an “initial response” and were thus randomized to the prednisone and tamoxifen arms (18 patients each) (**Figure 1**).

The baseline characteristics of the patients included in the two groups are summarized in **Tables 1** and **2**. The patients’ demographic characteristics were similar, and so were their main clinical manifestations at the time of disease onset. No substantial differences were found in acute-phase reactant levels, autoantibody positivity, and renal function tests, as well as in the prevalence of ureteral obstruction and acute renal failure (**Table 1**). Prior to study entry, ureteral decompression had been performed using either surgical ureterolysis or conservative techniques such as placement of ureteral stents or nephrostomy tubes; the proportions of patients who had been treated using either technique did not differ between

the two groups. Two patients (both in the prednisone group) with unilateral obstruction did not undergo ureteral decompression (**Table 1**).

The main characteristics of the retroperitoneal mass on CT or MRI studies, such as the prevalence of perianeurysmal forms, the maximal thickness of the tissue around the abdominal aorta and the iliac arteries, and the frequency of involvement of the inferior vena cava, were also similar in the two groups. IRF was distributed around the periaorto-iliac axis in almost all patients. None of the enrolled patients had atypical localizations such as perirenal, peri-pancreatic or (isolated) pelvic (**Table 2**).

Remission by the end of treatment

The primary end-point of the study was the rate of patients considered to be in a state of disease remission by the end of treatment. All of the 18 patients randomized to receive prednisone completed the 8-month course of therapy; one of them never achieved remission, because he never remained stent or nephrostomy-free (hydronephrosis soon reappeared after every attempt to remove the drainages) despite the complete disappearance of symptoms and the marked reduction in his acute-phase reactant levels. (**Table 3**). Overall, 17 of the 18 patients treated with prednisone (94.4%) were in remission by the end of treatment.

In the tamoxifen group, only 11 of the 18 patients (61.1%) were in remission by the end of treatment. The difference in remission rate between the prednisone and the tamoxifen arms was statistically significant ($p=0.04$). The seven tamoxifen-treated patients who were considered treatment failures showed disease relapses occurring at different times during treatment (from the 2nd to the 8th month post-randomisation), with clinical manifestations ranging from the reappearance of disease-related symptoms (particularly pain) to the

reappearance of hydronephrosis or the enlargement of the mass on CT/MRI. Interestingly, five of the seven patients (71%) with treatment failure were female. The details of the manifestations characterizing treatment failures are reported in **Table 3**.

Relapses in the tamoxifen-treated patients were all effectively treated with reintroduction of corticosteroids, alone or in combination with immunosuppressants; some of the patients are still on low-dose steroids at the time of this writing. The prednisone-treated patient who did not achieve remission was left on low-dose steroids and repeat substitutions of his stents/nephrostomies.

Secondary end-points

After randomization, the ureteral stents and nephrostomy tubes were removed at different times, at discretion of the clinician; the timing of stent removal was mainly based on the clinical course of the patient, the presence of stent/tube-related complications (bleeding, infections, pain), and the observation of reduction in size of the mass on CT/MRI. In the tamoxifen group, the stents/nephrostomies were removed after a median of 5 months (range 1-8 months), whereas in the prednisone group after a median of 6 months (range 2-8 months). In all patients with treatment failures characterized by relapsing hydronephrosis, the stents were re-placed; two patients (both in the tamoxifen arm) then underwent surgical ureterolysis.

Renal function improved in all patients who presented with renal failure and then achieved sustained disease remission. The improvement in renal function tests such as serum creatinine and estimated GFR was comparable in the two groups (data not shown). Only one patient (M, 75 years old), treated with tamoxifen, who ended therapy with a moderate

chronic renal impairment, later progressed to end-stage renal disease (despite no overt disease relapse) and started hemodialysis 6.5 years after being enrolled into the study.

The modification in size of IRF (baseline vs end of treatment or time of relapse) was calculated as a percentage variation of the maximal mass thickness at the aortic and iliac levels. The median change at the aortic level was a reduction of 50% (range, 14% to 100%) in the prednisone group and 40% (range, -33% to 85%) in the tamoxifen group ($p=0.05$). The median variation at the iliac level was a reduction of 60% (0%-82%) in the prednisone group and of 36% (range, -40% to 73%) in the tamoxifen group ($p=0.02$).

Treatment-related toxicity was more evident in the prednisone arm, whereas the side-effects associated with the use of tamoxifen were unquestionably mild. Common steroid-related side effects such as weight gain, moderate edema and hypercholesterolemia were observed in almost all of the treated patients. The median weight gain during treatment was of 2kg in the tamoxifen group and 7kg in the prednisone group ($p=0.001$). Additionally, two patients per group developed diabetes (in the tamoxifen-treated patient diabetes came up soon after the first month of prednisone therapy). Tamoxifen-related side effects included reduced libido, vaginal bleeding and hair loss, but they were transient and never required drug withdrawal.

Of the 11 and 17 patients who had achieved remission in the tamoxifen and prednisone groups, 3 (27%) and 4 (24%) respectively developed post-treatment relapses. Relapses occurred at varying times after the end of treatment; the median time from the end of treatment to relapse was 36 (6-93) months in the three patients who had been treated with tamoxifen and 23 (4-31) months in the patients who had been treated with prednisone (p not significant).

When considering relapses occurring both during and after treatment, there was a longer relapse-free survival in the prednisone group than in the tamoxifen group; the difference ($p=0.19$) did not reach statistical significance, probably because of the low number of patients enrolled (**Figure 2**).

At the end of follow-up, all of the patients treated with prednisone were alive whereas one of those treated with tamoxifen died at the age of 83 years of pancreatic cancer (8 years after the initial diagnosis of IRF).

Discussion

The present study shows that, in patients with IRF who received induction therapy with prednisone for one month, an 8-month course of prednisone is superior than an 8-month course of tamoxifen in inducing disease remission. This is the first randomized controlled trial ever performed in IRF patients; our results confirm previous findings showing the positive response of IRF to steroid therapy (15, 16), whereas they cast doubts on the efficacy of tamoxifen, which had been purported in numerous case reports and in a relatively large prospective case series (20, 22, 23, 26); in the latter study, 15 of the 19 patients enrolled showed clinical improvement within weeks to months, and CT scan at four months demonstrated moderate to significant mass regression in 12 patients; additionally, in 10 patients with a median follow-up of 15 months, there was continued mass regression. However, relatively few patients in this series had significant renal involvement, and the effects of therapy on post-treatment relapse rates are unknown, as most patients were still on therapy at the final analysis (27).

The mechanisms through which tamoxifen could exert its activity in IRF have only been hypothesized: tamoxifen is an anti-estrogen drug, but immunohistochemical analyses of IRF biopsies have revealed no receptors for estrogens, therefore it has been proposed that this drug acts independently of the estrogen-mediated pathway. Anti-angiogenic and anti-inflammatory effects have been proposed; moreover, tamoxifen could modify the growth factor balance in a way that results in inhibition of fibroblast proliferation and collagen deposition (23). However, all of these mechanisms remain hypothetical. Glucocorticoids are able to suppress the inflammatory reaction associated with IRF through the inhibition of cytokine and chemokine secretion, as well as a number of other anti-inflammatory mechanisms; the observation that corticosteroid-responding IRF patients may show marked

regression of the retroperitoneal mass has led to the hypothesis that steroids not only suppress inflammation but also interfere with fibrogenesis through the impairment of fibroblast proliferation and function.

In our study, the response to prednisone was rapid in most patients; unfortunately, some of them had to stop the treatment protocol early because of acute steroid-related toxicity. After randomization, a significant proportion of patients under tamoxifen treatment developed disease relapse, which was clinically characterized in most cases by recurrent pain, imaging evidence of relapsing hydronephrosis, often accompanied by an increase in acute-phase reactant levels; conversely, only one of the patients treated with prednisone did not achieve remission (he never remained ureteral stent-free despite the disappearance of disease-related symptoms and the normalization of acute-phase reactants). Not only was this difference in remission rate between the two groups statistically significant, but the prednisone-treated patients also showed a trend to a longer relapse-free survival, calculated as the time from remission to the first relapse (occurred either during or after treatment). In addition, prednisone induced a more pronounced regression in size of the retroperitoneal mass. Other parameters did not differ between the two treatment limbs, such as renal function modifications and the ultimate renal outcome: this is probably because most patients complied with a regular and close follow-up schedule and therefore relapses causing ureteral obstruction were recognized early and treated appropriately. This observation underlines the importance of choosing a composite end-point to evaluate the efficacy of treatment in IRF. Improvement in clinical manifestations such as pain or systemic symptoms is often very subjective and cannot be the sole criterion to define disease remission. Similarly, the resolution of hydronephrosis may occur despite an ongoing uncontrolled inflammatory reaction. On the other hand, regression in size of the mass may

not be necessary to the achievement of remission, since it has been shown that corticosteroids may induce disappearance of symptoms and normalization of the acute-phase reactants despite the lack of mass shrinkage; this is probably because, in largely fibrotic retroperitoneal masses, corticosteroids suppress the inflammatory foci without inducing a significant modification in size of the whole mass.

Overall, treatment with tamoxifen was well tolerated, with only a few side effects, whereas the usual steroid-related side effects were observed in most of the patients treated. This is a remarkable point, especially for frequently relapsing patients who may ultimately be exposed to repeat treatment courses, as well as for those who have contraindications for a prolonged steroid treatment such as diabetes, osteoporosis, and overt cardiovascular disease. Based on these considerations, on observed benefit in previous reports and in a fraction of our patients, we believe that tamoxifen should be considered a feasible therapeutic option for selected IRF cases. Moreover, further studies are warranted to assess whether it can be used as a maintenance agent in patients who have achieved sustained remission following corticosteroid therapy.

Although prednisone induced disease remission in more than 90% of the patients, a significant proportion (~25%) of them developed relapses; this has also been observed in previous studies (15, 16) and confirms the chronic inflammatory nature of the disease. This opens the question as to whether steroid treatment should be prolonged for more than nine months and whether relapsing patients also need to receive steroid-sparing agents such as methotrexate or azathioprine. At our centre, an open-label trial is ongoing to evaluate the efficacy of prednisone plus methotrexate in relapsing IRF patients.

Overall, the outlook of IRF patients in our study was good, with preserved long-term renal function and generally good clinical condition. The disease did not either impact overall

survival; at the end of follow-up all but one patient were alive, with the cause of death in the deceased patient (pancreatic cancer) being presumably not related to IRF or its treatment. This shows that IRF may have a very good prognosis if recognized early and treated appropriately with a combined interventional/surgical and medical approach.

In conclusion, the present study demonstrates that, in newly diagnosed IRF patients who underwent ureteral decompression and a 1-month induction therapy with prednisone, an 8-month course of prednisone is more effective than an 8-month course of tamoxifen in inducing sustained disease remission.

Acknowledgments

I gratefully acknowledge my dearest collaborators and friends Alessandra Palmisano and Federico Alberici for their valuable contribution to this study, my mentor prof Carlo Buzio for his continuous help and support, and our nurse Adonella Bondavalli for her patience.

I would also like to thank all the patients with IRF who agreed to be enrolled into this trial.

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	Prednisone arm (n=18)	Tamoxifen arm (n=18)	<i>P value</i>
Male gender, <i>n (%)</i>	12 (67%)	11 (61%)	n.s.
Age, median (range)- <i>years</i>	56 (37-84)	61 (38-75)	n.s.
Abdominal/back pain, <i>n(%)</i>	16 (89%)	17 (94%)	n.s.
Systemic symptoms [†] , <i>n(%)</i>	15 (83%)	13 (72%)	n.s.
Testicular symptoms [‡] , <i>n(%)</i>	7/12 (58%)	6/11 (55%)	n.s.
Constipation, <i>n(%)</i>	6 (33%)	4 (22%)	n.s.
ESR, median (range)- <i>mm/h</i>	65.5 (15-122)	61.5 (8-120)	n.s.
CRP, median (range)- <i>mg/L</i>	26.5 (3.4-75.5)	27.5 (4.0-102.0)	n.s.
Hb, median (range)- <i>g/dL</i>	12.5 (8.6-14.4)	12.4 (9.6-15.6)	n.s.
Positive ANA, <i>n (%)</i>	10 (56%)	6 (33%)	n.s.
sCreatinine, median (range), <i>mg/dL</i>	1.55 (0.7-11.5)	1.45 (0.6-9.0)	n.s.
Ureteral obstruction, <i>n(%)</i>	14 (78%)	13 (72%)	n.s.
<i>Unilateral, n(%)</i>	5/14 (36%)	3/13 (23%)	n.s.
<i>Bilateral, n(%)</i>	9/14 (64%)	10/13 (77%)	n.s.
Acute renal failure, <i>n(%)</i>	8/18 (44%)	9/18 (50%)	n.s.
Retroperitoneal biopsy, <i>n(%)</i>	10 (56%)	10 (56%)	n.s.
<i>Ureteral decompression technique[¶]</i>			
Surgical ureterolysis, <i>n(%)</i>	3/14 (21%)	4/13 (31%)	n.s.
Stent/nephrostomy, <i>n(%)</i>	9/14 (64%)	9/13 (69%)	n.s.
No procedure, <i>n(%)</i>	2/14 (14%)	0	n.s.

Table 1: Main clinical and laboratory characteristics of the randomized patients at the time of disease onset.

[†]Systemic symptoms include: anorexia, weight loss, fatigue, low-grade fever; [‡]Testicular symptoms include: testicular pain, varicocele, hydrocele; [¶] the *n (%)* of patients undergoing ureteral decompression is calculated out of the *n* of patients with ureteral involvement

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Hb: haemoglobin; ANA: anti-nuclear antibodies; n.s. not significant (>0.05)

	Prednisone arm (n=18)	Tamoxifen arm (n=18)	P value
Perianeurysmal form, <i>n</i> (%)	4 (22%)	3 (17%)	n.s.
Aortic diameter (mm), median (range)	20 (16-55)	19 (12-50)	n.s.
<i>Localisation</i>			
Periaorto-iliac, <i>n</i> (%)	17 (94%)	17 (94%)	n.s.
Isolated periaortic, <i>n</i> (%)	0	1 (6%)	n.s.
Isolated peri-iliac, <i>n</i> (%)	1 (6%)	0	n.s.
Pericaval involvement, <i>n</i> (%)	11 (61%)	11 (61%)	n.s.
<i>Maximal mass thickness (mm)</i>			
Aortic level, median (range)	20 (0-32)	16 (5-52)	n.s.
Iliac level, median (range)	16 (8-30)	14 (0-60)	n.s.

Table 2: Main radiological characteristics of idiopathic retroperitoneal fibrosis at the time of disease onset, assessed by computed tomography or magnetic resonance imaging.

n.s. not significant (>0.05)

Patient (gender, age)	Time of relapse (month after randomisation)	Diagnosis of relapse
<i>Prednisone arm</i>		
M, 56	3 rd month	Bilateral hydronephrosis
<i>Tamoxifen arm</i>		
M, 47	2 nd month	Back pain, raised ESR (58 mm/h) and CRP (31 mg/L)
M, 56	8 th month	Back pain, left-sided hydronephrosis, raised ESR (32 mm/h)
F, 61	4 th month	Enlarged mass on CT, raised ESR (28 m/h)
F, 60	7 th month	Back pain, fatigue, raised ESR (42 mm/h) and CRP (16 mg/L)
F, 63	8 th month	Bilateral hydronephrosis, enlarged mass on MRI
F, 71	4 th month	Left-sided hydronephrosis, raised ESR (53 mm/h) and CRP (42 mg/L)
F, 59	5 th month	Back pain, left-sided hydronephrosis

Table 3. Characteristics of the patients who presented treatment failures in the two arms.

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CT: computed tomography; MRI: magnetic resonance imaging

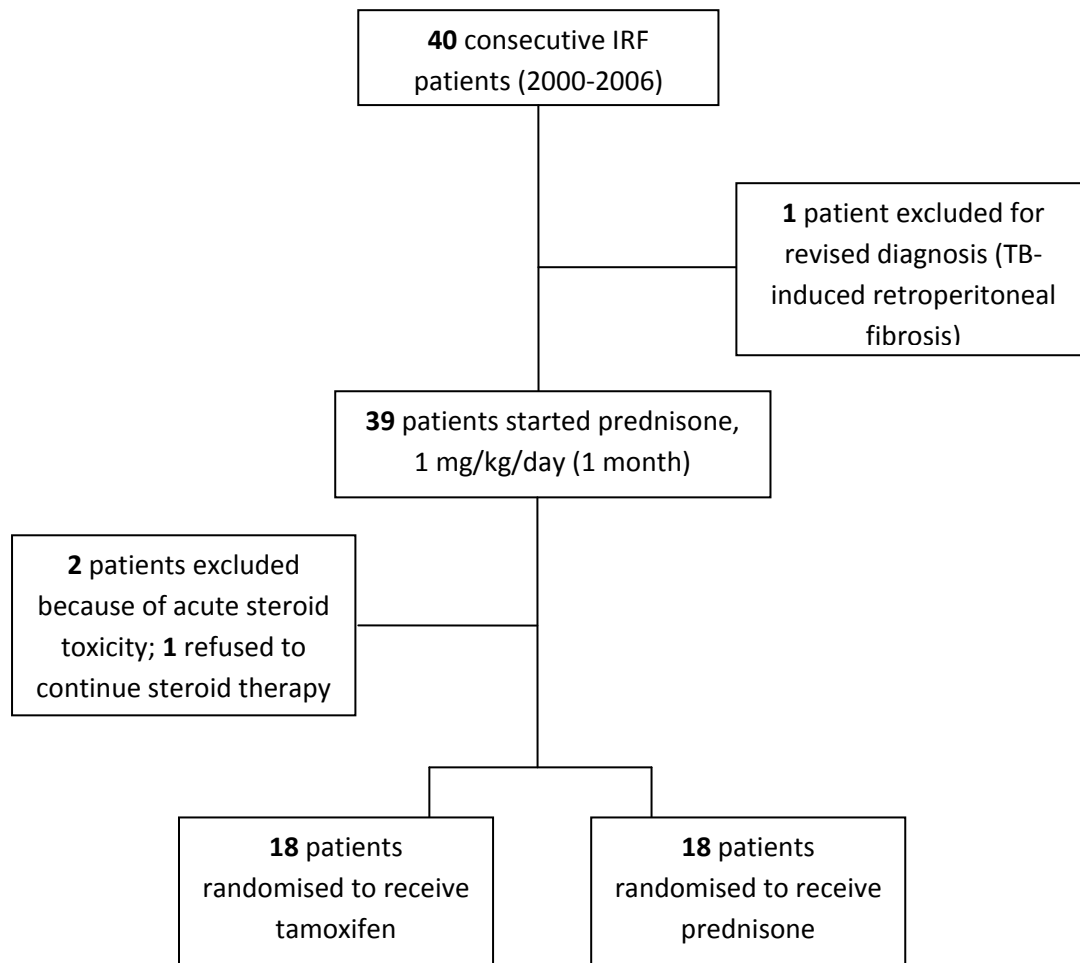


Figure 1. Overview of the study.

IRF: idiopathic retroperitoneal fibrosis; TB: tuberculosis

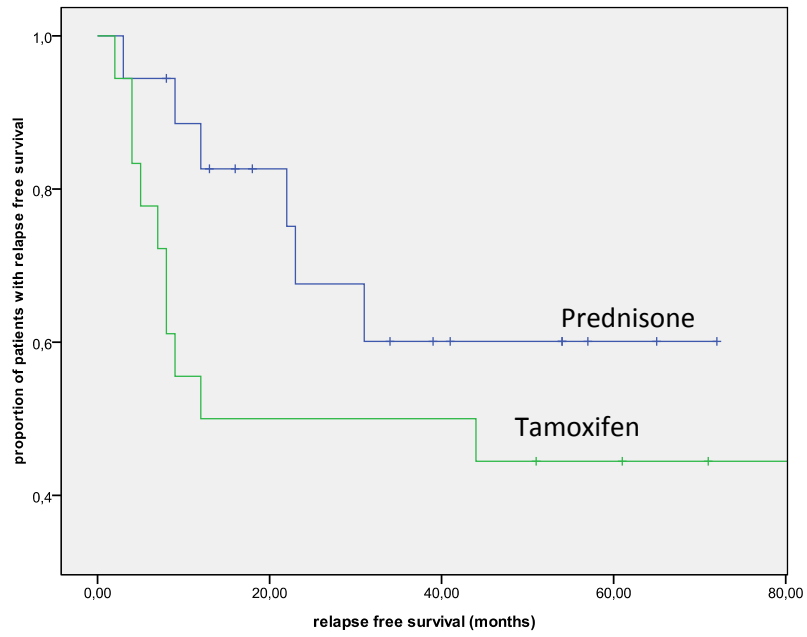


Figure 2. Kaplan-Meier estimate of the relapse-free survival in patients randomized to receive prednisone or tamoxifen.