Prednisone versus tamoxifen in patients with idiopathic retroperitoneal fibrosis: an open-label randomised controlled trial

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Summary

Background Glucocorticoids are the mainstay of treatment of idiopathic retroperitoneal fibrosis, but they often have substantial toxic effects. Several reports have suggested tamoxifen as an alternative to glucocorticoids. We compared the efficacy of prednisone with that of tamoxifen in maintainance of remission in patients with idiopathic retroperitoneal fibrosis.

Methods In this open-label, randomised controlled trial, we enrolled patients aged 18–85 years with newly diagnosed idiopathic retroperitoneal fibrosis at the Parma Hospital, Parma, Italy, between Oct 1, 2000, and June 30, 2006. After induction therapy with 1 mg/kg daily of prednisone for 1 month, the patients who achieved remission were randomly assigned to receive tapering prednisone (initial dose 0·5 mg/kg daily) for 8 months or tamoxifen (fixed dose 0·5 mg/kg daily) for 8 months. The sequence of randomisation (1:1), blocked in groups of two and four (with block size randomly selected), was generated by the trial statistician with a computer programme. After the end of treatment, the patients were followed up for an additional 18 months. Neither patients nor those giving interventions or analysing the data were masked to group assignment. The two radiologists who assessed CT and MRI scans were masked. The primary endpoint was the relapse rate by the end of treatment (month 8), which was analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00440349.

Findings After induction therapy, 36 of the 40 enrolled patients achieved remission and were randomly assigned to treatment (18 per group). One patient (6%) in the prednisone group and seven patients (39%) in the tamoxifen group relapsed by the end of treatment (difference –33% [95% CI –58 to –8, p=0·0408]. The difference in relapse rate between the groups was sustained after the additional 18-month follow-up: the 26-month estimated cumulative relapse probability was 17% with prednisone and 50% with tamoxifen (difference –33% [–62 to –3, p=0·0372]). Cushingoid changes and grade 2 hypercholesterolaemia were more common in the prednisone group than in the tamoxifen group (p=0·0116 and p=0·0408, respectively).

Interpretation Prednisone is more effective in prevention of relapses than is tamoxifen in patients with idiopathic retroperitoneal fibrosis. Therefore, prednisone should be considered as first-line treatment for patients with newly diagnosed idiopathic retroperitoneal fibrosis.

Funding Parma University Hospital.

Introduction

Idiopathic retroperitoneal fibrosis is a rare disease, characterised by the presence of a fibroinflammatory tissue that surrounds the abdominal aorta and the iliac arteries, and often entraps the ureters. The idiopathic form accounts for more than two-thirds of all cases of retroperitoneal fibrosis, with the remainder being secondary to different causes, such as drugs, tumours, infections, radiotherapy, and rare forms of histiocytosis such as the Erdheim-Chester disease.[1,2] Idiopathic retroperitoneal fibrosis is histologically characterised by abundant fibrosis and a mononuclear-cell inflammatory infiltrate mainly composed of lymphocytes, plasma cells, and macrophages.[3,4] Clinical manifestations include abdominal or back pain, systemic symptoms (eg, fatigue, weight loss), and, less frequently, constipation, testicular pain, and claudication. Ureteral obstruction occurs in about 60–80% of cases and often causes acute renal failure.[5–7]

The treatment of idiopathic retroperitoneal fibrosis is still empirical since no randomised trials have been done so far. Anecdotal cases of spontaneous resolution have been reported,[8–10] and a few patients with asymptomatic disease not affecting adjacent structures might need only monitoring. With the exception of these rare cases, medical treatment is usually necessary in patients with active disease. Glucocorticoids are deemed the mainstay of therapy, but their optimum dose and duration are unknown. They induce rapid symptom remission, reduction in acute-phase reactant values, and often shrinkage of the disease, but they have substantial side-effects.[11,12] These properties make glucocorticoids ideal as induction treatment, provided that an effective maintenance regimen is available.

Other immunosuppressive drugs (eg, mycophenolate mofetil, azathioprine)[13–17] have been successfully used together with glucocorticoids, but the superiority of these combination therapies to glucocorticoids alone is still unproven.[14]

On the basis of the observed benefit in desmoid tumours, which are characterised by fibroblast proliferation, tamoxifen has been used for idiopathic retroperitoneal fibrosis in various case reports and case series.[18–22] Because these cases had a favourable outcome and the drug tolerability was good, tamoxifen has become an attractive therapeutic option for this disease. We compared the efficacy of prednisone with that of tamoxifen in prevention of relapses in patients with newly diagnosed idiopathic retroperitoneal fibrosis who had received induction treatment with prednisone.

Methods

Patients

In this open-label, randomised controlled trial, we enrolled all patients meeting the eligibility criteria, diagnosed at or referred to the Department of Clinical Medicine and Nephrology of Parma Hospital, Parma, Italy, between Oct 1, 2000, and June 30, 2006. Key inclusion criteria were a new diagnosis of idiopathic retroperitoneal fibrosis and an age of 18–85 years; we also enrolled patients with perianeurysmal retroperitoneal fibrosis, since this form is also idiopathic.[7,23] Key exclusion criteria were previous treatment for retroperitoneal fibrosis, pregnancy, active infections or malignancies, known hypersensitivity to the study drugs, uncontrolled diabetes, and retroperitoneal fibrosis secondary to known causes.[1] To rule out drug-related retroperitoneal fibrosis, we reviewed the patient medication history searching for drugs associated with the disease, particularly methysergide, pergolide, ergotamine, and methyldopa.[1] We did a Quantiferon test (Cellestis Limited, Chadstone, Melbourne, VIC, Australia) and urine (or sputum, when available) cultures for mycobacteria to exclude tuberculosis-related forms. We also screened for underlying tumours by testing various neoplastic markers (including carcinoembryonic antigen [CEA], carbohydrate antigen [CA] 19-9, α-fetoprotein, prostate-specific antigen [PSA]) and fecal occult blood, and did chest radiographs. Finally, to rule out Erdheim-Chester disease, we did bone scintigraphy if retroperitoneal fibrosis was also perirenal (highly suggestive of the disease)[24] or if the patient reported bone pain or other manifestations of Erdheim-Chester disease. Idiopathic retroperitoneal fibrosis was diagnosed by CT or MRI, following commonly accepted radiological criteria;[3,5,7] retroperitoneal biopsy was done in patients with suspected secondary forms or atypical mass localisation,[25] and in those undergoing surgical ureterolysis.

The study was done in accordance with the Declaration of Helsinki. The protocol was approved by the Ethical Committee of Parma Hospital, Italy. All patients signed an informed consent form.

Randomisation and masking

Patients who achieved remission after induction therapy were randomly assigned in a 1:1 ratio to receive prednisone or tamoxifen. The sequence of randomisation, blocked in groups of two and four (with the block size being randomly selected), was generated by the trial statistician with a computer programme, and subsequently put in sealed, sequentially numbered opaque envelopes. AV, AP, FA, and CB were involved in both patient enrolment and assignment to trial groups. Neither the participants nor those giving the interventions or analysing data were masked to group assignment; conversely, the two radiologists who assessed the CT and MRI scans were masked to group assignment and clinical status of patients.

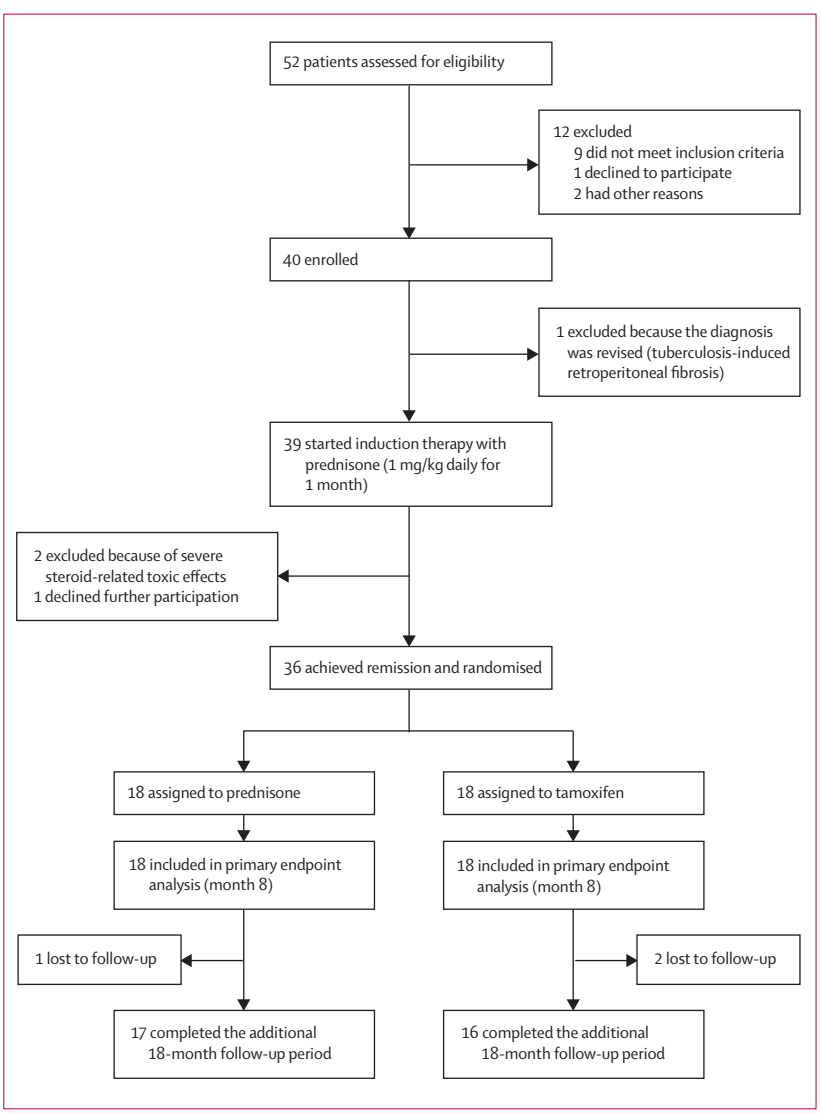

Figure 1: **Trial profile**

	Prednisone group (n=18)	Tamoxifen group (n=18)
Men	12 (67%)	11 (61%)
Age (years)	56 (37–84)	61 (38–75)
Clinical manifestations		
Abdominal or back pain	16 (89%)	17 (94%)
Systemic symptoms*	15 (83%)	13 (72%)
Testicular symptoms†	7/12 (58%)	6/11 (55%)
Constipation	6 (33%)	4 (22%)
Laboratory findings		
Erythrocyte sedimentation rate (mm/h)	65·5 (15–122)	61·5 (8–120)
C-reactive protein concentration (mg/L)	26·5 (3·4–75·5)	27·5 (4·0–102·0)
Serum creatinine concentration (μmol/L)	137·0 (61·9–1016·6)	128·2 (53·0–795·6)
Ureteral obstruction		
Overall	14 (78%)	13 (72%)
Unilateral	5/14 (36%)	3/13 (23%)
Bilateral	9/14 (64%)	10/13 (77%)
Acute renal failure	8 (44%)	9 (50%)
Characteristics of RPF at CT or MRI		
Perianeurysmal form‡	4 (22%)	3 (17%)
Abdominal aorta diameter (mm)	20 (16–55)	19 (12–50)
Localisation		
Periaortoiliac	17 (94%)	18 (100%)
Isolated periaortic	0	0
Isolated peri-iliac	1 (6%)	0
Pericaval involvement	11 (61%)	11 (61%)
Maximal RPF thickness (mm)		
Periaortic	20 (0–32)	16 (5–52)
Peri-iliac	16 (8–30)	14 (5–60)
Retroperitoneal biopsy	10 (56%)	10 (56%)
Ureteral decompression technique§		
Surgical ureterolysis	3/14 (22%)	4/13 (31%)
Stents or nephrostomies	9/14 (64%)	9/13 (69%)
No procedure	2/14 (14%)	0
Diagnosis-to-treatment interval¶ (months)	3 (1–14)	2·5 (1–20)

Continuous variables are expressed as median (range) and categorical variables as n (%) or n/N (%). RPF=retroperitoneal fibrosis. CT=computed tomography. MRI=magnetic resonance imaging. *Systemic symptoms include fatigue, anorexia, weight loss, low-grade fever, diffuse myalgias, and arthralgias. †Testicular manifestations include testicular pain, varicocele, and hydrocele. ‡Perianeurysmal indicates idiopathic retroperitoneal fibrosis surrounding an aneurysmal abdominal aorta. §This percentage is calculated on the total number of patients with ureteral obstruction. ¶The diagnosis-to-treatment interval indicates the time elapsed between the diagnosis and the start of therapy.

Table 1: **Demographic and clinical characteristics of the patients at study entry**

Procedures

At study entry, the patients underwent physical examination, routine laboratory tests (including blood cell count, renal and liver function tests, serum electrolytes, fasting glucose, lipid profile, urinalysis, erythrocyte sedimentation rate [ESR], and C-reactive protein [CRP]), chest radiograph, and abdominal CT or MRI.[6] If hydronephrosis was present, ureteral decompression had to be done before the start of medical treatment by either conservative procedures (eg, stents, nephrostomies) or surgical ureterolysis. Subsequently, the patients received 1 mg/kg daily of prednisone (maximum 80 mg daily) for 1 month, at the end of which they were reassessed: those who showed symptom remission and near normalisation of ESR and CRP values[12] (ie, normalisation or reduction to <30% of the baseline values) were randomly assigned to receive prednisone or tamoxifen. Those who showed only partial clinical or laboratory improvement continued prednisone at the same dose for another month and were then reassessed for randomisation.

The patients assigned to the prednisone group received 0·5 mg/kg daily of prednisone for month 1 after randomisation, 0·25 mg/kg daily for months 2–3, 0·20 mg/kg daily for month 4, 0·15 mg/kg daily for month 5, 7·5 mg daily for month 6, 5 mg daily for month 7, 2·5 mg daily for the first half of month 8, and 2·5 mg on alternate days for the second half of month 8. Those assigned to the tamoxifen group withdrew prednisone within 2 weeks and received tamoxifen at a fixed dose (0·5 mg/kg daily, maximum 40 mg per day) for months 1–8. Proton-pump inhibitors, calcium, vitamin D, and bisphosphonates were also given. Both prednisone and tamoxifen were withdrawn at the end of month 8. The timing of stent or nephrostomy removal was left at the discretion of the treating clinician. After the end of the experimental period (month 8), the patients were followed up for an additional 18 months. Clinical examination and routine laboratory tests were done every 1–2 months during the experimental period (months 1–8) and every 3–6 months during the post-treatment follow-up (months 9–26). Abdominal CT or MRI was done at baseline, month 4, end of treatment, and every 6–12 months thereafter. The same imaging method (either CT or MRI) was used for every patient throughout the study.

The primary endpoint was the relapse rate by the end of treatment (month 8). The diagnosis of relapse was based on the presence of recurrent or new-onset disease-related symptoms, hydronephrosis, or mass enlargement on CT or MRI (≥20% increase in mean maximal thickness as compared with the previous scans), or any combination of these three conditions. An increase in ESR or CRP values (≥50% of the values recorded at the previous visit) was required to confirm relapse in patients who showed only disease-related symptoms but did not have hydronephrosis or mass enlargement. Isolated increases in ESR or CRP values were not sufficient to diagnose relapse. Hydrocele, varicocele, and erectile impairment were not considered for the diagnosis of relapse, because their course is often independent of that of retroperitoneal fibrosis. The treatment of relapses was left at the discretion of the treating clinician.

Secondary endpoints included the 8-month change in renal function, ESR and CRP values, and size of retroperitoneal fibrosis; we also examined the relapse frequency and the secondary endpoints during the post-treatment follow-up (months 9–26) in the patients who were in remission at the end of the experimental period, and estimated the 26-month cumulative probability of relapse in all randomly assigned patients. Renal function

was assessed by measure of serum creatinine and estimated GFR (eGFR) with the modification of diet in renal disease (MDRD) formula.[26] We assessed the change in size of retroperitoneal fibrosis by calculating variations in the maximal mass thickness at the infrarenal aorta and common iliac artery levels; mean maximal thickness was the average of the above two measures. CT and MRI scans were assessed by two independent radiologists; discrepancies in their assessments were resolved by consensus.

Treatment-related toxic effects were assessed at every visit by a checklist of standardised items, measurement of blood pressure and bodyweight, and routine laboratory tests. Adverse events were graded following the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.[27]

We did immunohistochemical analyses to assess IgG4+ plasma cell infiltration. Unstained retroperitoneal biopsy samples were analysed with primary antibodies for IgG4 (Zymed, San Francisco, CA, USA, cod 05-3800, clone HP 6025, dilution 1:100, pretreatment pH 9 waterbath 95°C for 40 min) and for CD138 (Bio Care Medical, Concord, CA, USA, cod CM 167 C, clone B-A38, dilution 1:200, pretreatment pH 9 waterbath 95°C for 40 min). After immunohistochemical detection, the tissue sections were mildly counterstained with Harris haematoxylin. IgG4+ plasma cell infiltration was considered high when the plasma cell ratio of IgG4+ to total CD138+ was lower than 30%.[28]

Statistical analysis

We estimated that 18 patients per group would achieve about 80% power to detect a difference between a relapse rate of 5% with prednisone and 50% with tamoxifen, using a two-sided Fisher's exact test with a significance level of 0·05.[29,30] All analyses of data until month 26 after randomisation were done by intention to treat. Categorical data were compared by the Fisher's exact test, and continuous data by the Mann-Whitney test. Because of the censoring, we used the Kaplan-Meier method to estimate the 26-month cumulative probability of relapse, which was compared between the two groups with the log-rank test. A two-sided p value less than 0·05 was considered significant. All analyses were done with Stata Statistical Software realease 11. The study is registered with ClinicalTrials.gov, number NCT00440349.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 40 patients enrolled (figure 1), one was excluded because the diagnosis was revised (this patient was the subject of a case report).[31] Of the 39 patients who started induction prednisone therapy, three were excluded. The

	Month*	Pain or systemic symptoms†	ESR (mm/h)	CRP (mg/L)	New-onset or recurrent ureteral obstruction	Mass thickness (mm)	Treatment for relapse
Prednisone group							
Man, 56 years	1	Absent	Stable (12 to 13)	Increased (4·1 to 12·6)	Bilateral	Stable (21 to 21)	Placement of nephrostomies (no change in medical treatment)
Tamoxifen group							
Man, 47 years	2	Present	Increased (6 to 58)	Increased (2·0 to 31·0)	Absent	Decreased (26 to 16·5)	Switch to prednisone
Man , 56 years	8	Present	Increased (25 to 38)	Stable (8·0 to 5·7)	Unilateral	Increased (6·5 to 8)	(lost to follow-up)
Woman, 61 years	4	Present	Increased (13 to 28)	Increased (0·3 to 11·7)	Unilateral	Stable (12·5 to 11·5)	Tamoxifen for 4 additional months, then switch to prednisone
Woman, 60 years	7	Present	Increased (42 to 63)	Stable (15·8 to 21·4)	Absent	Stable (9 to 9)	Switch to prednisone
Woman, 63 years	8	Absent	Increased (5 to 16)	Increased (0·5 to 11·2)	Bilateral	Increased (11 to 18)	Ureterolysis and switch to prednisone
Woman, 71 years	4	Absent	Increased (3 to 53)	Increased (5·0 to 42·0)	Absent	Increased (15 to 18)	No change in treatment (the patient refused steroids)
Woman, 59 years	5	Present	Stable (11 to 8)	Stable (6·0 to 5·0)	Unilateral	Not available	Placement of stent and switch to prednisone

The values reported for ESR, CRP, and mass thickness indicate the change between the visit (or CT or MRI scan) preceding relapse and relapse itself. ESR=erythrocyte sedimentation rate. CRP=C-reactive protein level. MRI=magnetic resonance imaging. Increased, decreased or stable, with respect to ESR and CRP, denote variations higher than, lower than, or within 50% of the values recorded at the previous visit, respectively. Mass thickness was calculated as the average of the maximum thickness assessed at the lower abdominal aorta and common iliac artery levels. Increased, decreased, or stable, with respect to mass thickness, denote variations higher than, lower than, or within 20% of the values recorded at the previous CT or MRI scan, respectively. *Month refers to the month after randomisation at which relapse was diagnosed. †Systemic symptoms include: fatigue, anorexia, weight loss, low-grade fever, diffuse myalgias, and arthralgias.

Table 2: **Characteristics of the patients who developed relapses by month 8 after randomisation (primary endpoint)**

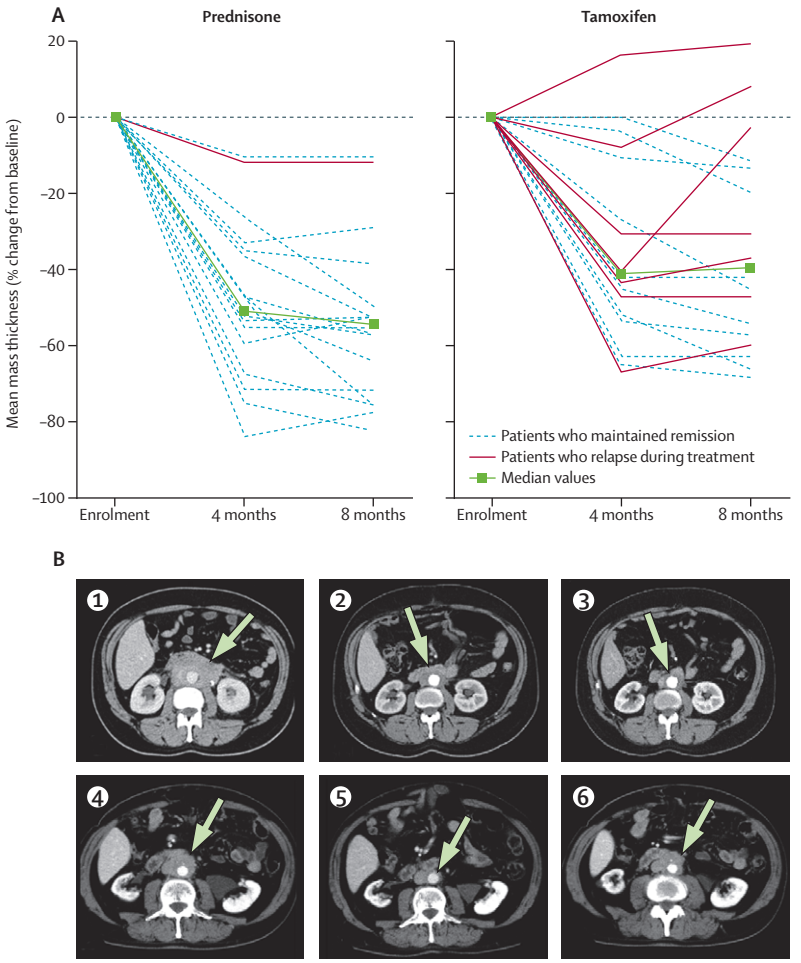

Figure 2: **Variations in size of idiopathic retroperitoneal fibrosis and representative CT scans**
(A) Percentage variations in the mean maximal thickness of the retroperitoneal mass during the treatment period in the prednisone and tamoxifen groups. Mean maximum thickness was calculated as the average of maximal peri-aortic and peri-iliac thickness. The reduction in mass thickness was significantly greater in the prednisone group than in the tamoxifen group, at month 4 (p=0·0462) and at month 8 after randomisation (p=0·0314). Comparisons were done according to the intention-to-treat principle. (B) (1–3) Abdominal contrast-enhanced CT scans in a patient treated with prednisone show that the periaortic retroperitoneal mass (1, arrow) markedly shrinks at month 4 after randomisation (2, arrow) and stabilises at the month-8 scan (3, arrow). (4–6) Abdominal contrast-enhanced CT scans in a patient treated with tamoxifen who developed relapse during treatment show that the periaortic tissue (4, arrow) is reduced in size at month 4 (5, arrow) and enlarges at relapse (6, arrow).

See Online for webappendix

remaining 36 completed the month of induction prednisone therapy, at the end of which they all achieved symptom remission and normalisation of ESR and CRP values, and were thus randomly assigned to receive prednisone or tamoxifen.

Demographic, clinical, and laboratory characteristics were well balanced between groups (table 1). The main imaging features of retroperitoneal fibrosis, the percentage of biopsy-proven diagnoses, and the diagnosis-to-treatment intervals were also similar. Ureteral decompression was done by surgical ureterolysis or conservative procedures (placement of ureteral stents or nephrostomies); the proportions of patients treated with either technique were also similar (table 1).

The primary endpoint was the relapse rate by the end of treatment (month 8) in patients who had achieved remission after induction therapy. One (6%) of the 18 prednisone-treated and seven (39%) of the 18 tamoxifen-treated patients developed relapses while on treatment (difference of −33% [95% CI −58% to −8%; p=0·0408]; webappendix p 1). The remaining patients were in remission at the end of treatment—ie, they were asymptomatic, had normal acute-phase reactants, had no hydronephrosis, and were stent-free or nephrostomy-free. Table 2 shows the main findings at the time of relapse. The only patient who relapsed during prednisone treatment developed recurrent bilateral hydronephrosis despite being asymptomatic and having normal acute-phase reactants. In the tamoxifen group, relapses were variably characterised by recurrent abdominal or lumbar pain, raised acute-phase reactants, hydronephrosis, and mass enlargement (table 2). Relapses were treated as reported in table 2. All patients who switched to prednisone ultimately achieved remission; two of them had an additional relapse and then received prednisone plus methotrexate. The patient who refused to switch to prednisone (woman, 71 years old) developed further disease progression, unilateral hydronephrosis, and was then lost to follow-up.

The webappendix (p 2) shows the variations in the main laboratory and imaging parameters during the study. Renal function at the end of the experimental period (month 8) did not differ significantly between groups (webappendix p 2). The median time from the start of treatment to removal of stent or nephrostomy was 5·0 months (range 2–8) in the prednisone group and 4·5 months (range 1–8) in the tamoxifen group (p=0·88). Equally, ESR and CRP values did not differ between groups (webappendix p 2). The reduction in mean mass thickness was greater in the prednisone group (p=0·0462 at month 4 after randomisation and p=0·0314 at the end of treatment); figure 2 shows percentage changes in mass thickness and representative CT scans, whereas absolute changes in peri-aortic and peri-iliac thickness are reported in the webappendix p 2.

Cushingoid changes were more common in the prednisone group (p=0·01; table 3), although they usually improved or subsided after prednisone withdrawal. One patient on tamoxifen had self-limiting vaginal bleeding. The median weight gain during treatment was 7 kg (range 1–10) in the prednisone group and 2 kg (−3 to 11) in the tamoxifen group (p=0·002). The frequencies of cardiovascular events, diabetes, hypertension, and urinary tract infections were similar; grade 2 hypercholesterolaemia was significantly more frequent in the prednisone group than in the tamoxifen group (p=0·0408).

In the follow-up after the experimental period, two (12%) of the 17 prednisone-treated and two (18%) of the 11 tamoxifen-treated patients who were in remission after 8 months developed post-treatment relapses by month

26 (p=1·00; webappendix p 1). These relapses occurred at months 13 and 26 in the prednisone group, and at months 15 and 26 in the tamoxifen group. Overall, the 26-month cumulative probability of relapse of all randomised patients was significantly lower in the prednisone group (17%) than in the tamoxifen group (50%; difference −33% [95% CI −62 to −3], p=0·0372; figure 3). Secondary endpoints during the follow-up period of 9–26 months did not differ (webappendix p 2).

Because of the long accrual time of this trial, most patients were followed up beyond the originally planned 26-month period; clinical data of 14 patients assigned to prednisone originally and 16 patients to tamoxifen were available. After month 26, relapses occurred in three of the prednisone-treated patients (months 28, 34, and 38) and two of the tamoxifen-treated patients (months 47 and 102). The median overall follow-up in the prednisone and tamoxifen groups was 57 months (range 9–80) and 61 months (9–112). One patient (who had received tamoxifen) developed end-stage renal disease, started haemodialysis at month 80, and died of pancreatic cancer at month 91. At last follow-up, all the remaining patients were alive and had good renal function; all but two were in remission, and ten (all of whom developed relapses) were still taking low-dose prednisone, alone or with methotrexate.

Time to relapse and change in size of retroperitoneal fibrosis of patients with peri-aneurysmal retroperitoneal fibrosis did not differ significantly from that of patients with non-aneurysmal disease (post-hoc analysis; data not shown).

None of our patients had signs or symptoms of extraretroperitoneal IgG4-related diseases (eg, sclerosing pancreatitis, cholangitis). To assess which cases of retroperitoneal fibrosis were IgG4-related, we analysed the available biopsy samples immunohistochemically. Four (29%) of the 14 studied cases showed high IgG4+ plasma cell infiltration (representative figures are shown in webappendix p 3). One of these patients received prednisone and three tamoxifen; all achieved remission and none of them relapsed during the 26-month follow-up after randomisation. The reduction in size of retroperitoneal fibrosis was 58%, 53%, and 0% in the three tamoxifen-treated patients, and 56% in the prednisone-treated patient.

Discussion

This study, the first randomised trial in retroperitoneal fibrosis to our knowledge (panel), compared the efficacy of prednisone and tamoxifen in maintainance of remission in patients who had received induction prednisone therapy. Induction therapy was very effective in obtaining symptom remission and normalisation of acute-phase reactants. Subsequently, we noted that the proportion of patients who developed relapses while being on treatment was significantly higher in the tamoxifen group than in the prednisone group, suggesting

	Prednisone group (n=18)	Tamoxifen group (n=18)	p value
Cardiac ischaemia infarction			
Grade 3	1 (6%)	0	1·00
Grade 4	0	1 (6%)	1·00
Fasting glucose at study entry (mmol/L)	4·8 (3·7–6·5)	5·1 (4·2–8·8)	0·18
Fasting glucose at month 8 (mmol/L)	4·8 (3·9–7·9)	5·2 (4·4–8·0)	0·09
Diabetes			
Grade 2	2 (11%)	1 (6%)	1·00
Grade 3	0	1 (6%)	1·00
Total cholesterol at study entry (mmol/L)	4·9 (3·6–7·0)	5·1 (3·4–6·9)	0·53
Total cholesterol at month 8 (mmol/L)	5·6 (4·2–6·9)	5·4 (3·5–8·2)	0·20
Hypercholesterolaemia			
Grade 1	8 (44%)	11 (61%)	0·51
Grade 2	7 (39%)	1 (6%)	0·04
Mean arterial blood pressure† at study entry (mm Hg)	103·3 (83·3–113·3)	98·3 (76·7–113·3)	0·21
Mean arterial blood pressure at month 8 (mm Hg)	100·0 (83·3–115)	98·3 (73·3–118·3)	0·58
Hypertension			
Grade 2	7 (39%)	5 (28%)	0·54
Urinary tract infection‡			
Grade 2	1 (6%)	1 (6%)	1·00
Grade 3	2 (11%)	3 (17%)	1·00
Bone fracture			
Grade 3	1 (6%)	0	1·00
Deep-vein thrombosis			
Grade 3	0	1 (6%)	1·00
Cushingoid changes§	10 (56%)	2 (11%)	0·01
Other¶	1 (6%)	3 (17%)	0·60

Continuous variables are presented as median (range) and categorical variables as n (%). *Adverse events were categorised according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3. †Mean arterial blood pressure was calculated as ([2x diastolic]+systolic)/3. ‡Two patients in the tamoxifen group and one in the prednisone group had two episodes each of grade 3 infection of the urinary tract. All the remaining patients had a single episode. §Cushingoid changes include: moon face, oedema, hirsutism, acne, easy bruising, as well as nervousness, insomnia, and other psychological effects. Patients with Cushingoid changes persisting for more than 4 months from the start of treatment were considered. ¶Other includes: oral candidiasis (one patient), vaginal bleeding (one patient), and reactive arthritis (one patient) in the tamoxifen group, and haematuria (one patient) in the prednisone group.

Table 3: **Adverse events at month 8 after randomisation***

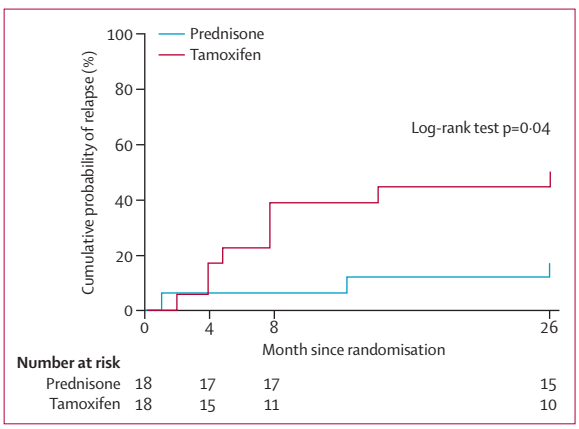

Figure 3: **Kaplan-Meier estimate of the time from randomisation to the first relapse in the two treatment groups**

Panel: **Research in context**

Systematic review

We searched PubMed without any date limits for full papers reporting studies of any kind on the treatment of idiopathic retroperitoneal fibrosis, with the terms "retroperitoneal fibrosis" and "treatment". We identified no randomised controlled trials or meta-analyses.

Interpretation

The use of prednisone or other glucocorticoids was reported in most studies (reports of single cases and retrospective and prospective uncontrolled trials);[11,12,15,32] the use of tamoxifen was mainly described in single case reports[18–21,33] and a few case series.[15,22] Findings from these case series suggested that tamoxifen could be effective in the treatment of idiopathic retroperitoneal fibrosis, and safer than glucocorticoids.[15,22] Our study, the first randomised trial to be done to our knowledge in patients with idiopathic retroperitoneal fibrosis, shows that prednisone is more effective than tamoxifen in controlling the disease, although the toxic effects of prednisone can be more pronounced than those of tamoxifen. We suggest that prednisone should be considered as first-line treatment for patients with newly diagnosed idiopathic retroperitoneal fibrosis.

that prednisone is better than tamoxifen in maintaining the remission achieved with induction therapy.

The patients who received prednisone also had a more pronounced shrinkage of retroperitoneal fibrosis. In this treatment group, mass thickness decreased on average by 50% at month 4, and stabilisation or slight further reduction was noted during the ensuing 4 months of treatment. Shrinkage of retroperitoneal fibrosis was also more pronounced during the first half of treatment in the tamoxifen group than during the ensuing 4 months, but then the mass tended to re-expand. We did not do CT or MRI at the time of randomisation to avoid the risks of too frequent procedures (an interval of 5 months from baseline to the first CT is similar to that chosen by other investigators[12,22,34]); therefore, we cannot appreciate the extent to which induction prednisone treatment contributed to mass reduction. However, as the clinical response of idiopathic retroperitoneal fibrosis to glucocorticoids usually occurs within a few weeks,[12,32] the mass shrinkage observed in both groups could have been also accounted for by induction therapy.

The rate of relapses after treatment was similar between the two groups; during the whole post-treatment follow-up (including the period after month 26), we noted relapses in five (29%) of the 17 patients and four (36%) of the 11 patients in remission at the end of treatment who had originally received prednisone and tamoxifen, respectively. In the largest studies in which prednisone alone was used in idiopathic retroperitoneal fibrosis (with initial doses of 30–60 mg daily), remission occurred in 92–100% of patients,[11,12,32] whereas the relapse rates ranged from 11–25%[11,32] to 72%.[12] Only one study[22] reported the use of tamoxifen monotherapy in a large series of patients (n=19); 15 patients (79%) showed symptom improvement and 12 (63%) showed mass shrinkage at the 4-month follow-up. During the whole follow-up, five (26%) patients had treatment failure because of persistent or recurrent symptoms or mass enlargement.

Similar to previous reports,[18–22] tamoxifen-related toxic effects were mild, whereas most prednisone-treated patients had side-effects related to steroids; prednisone also induced a greater weight gain and a higher incidence of severe hypercholesterolaemia than did tamoxifen. Additionally, two patients had to stop prednisone during induction therapy because of intolerable toxic effects. Bearing this in mind, and considering the good tolerability of tamoxifen and its efficacy at least some patients, this drug could still be regarded as an exploitable option for patients with idiopathic retroperitoneal fibrosis who have contraindications to steroids; the identification of predictors of response to tamoxifen treatment would be desirable to carefully select candidate patients.

Idiopathic retroperitoneal fibrosis is grouped with perianeurysmal retroperitoneal fibrosis and inflammatory abdominal aortic aneurysms under the umbrella term chronic peri-aortitis,[1,35] because these entities have similar clinical and histopathological aspects. However, their pathogenesis is probably different, because the perianeurysmal forms have a more pronounced male predominance, a more severe atherosclerotic component, and different immunogenetic determinants than does the idiopathic form.[36] Therefore, the response of these disorders to treatment can also differ. The patients with perianeurysmal retroperitoneal fibrosis enrolled in our study (seven of the 36 randomised patients) did not seem to have a peculiar clinical outcome, but larger numbers of patients are needed to address this issue.

Some forms of retroperitoneal fibrosis belong to the IgG4-related disease, an often systemic, steroid-responsive disorder whose histological features include intense IgG4+ plasma cell infiltration and marked fibrosis.[37,38] None of the study patients had typical extraretroperitoneal IgG4-related lesions, and the four patients (of the 14 analysed) who showed high IgG4+ plasma cell retroperitoneal infiltration all had a favourable outcome. However, the size of this subgroup is again too small to draw any conclusion.

Idiopathic retroperitoneal fibrosis has a likely immune-mediated pathogenesis, as documented by the intense inflammatory cell infiltration accompanying the fibrotic reaction, and the association with autoimmune diseases and with the HLA-DRB1*03.[1,3,39–41] Thus, different mechanisms might explain the effectiveness of glucocorticoids in idiopathic retroperitoneal fibrosis, including their ability to suppress cytokine and chemokine secretion and to interfere with fibrogenesis.[42,43] Tamoxifen is thought to exert oestrogen

receptor-independent antifibrotic and antiangiogenic effects,[22] but its precise mechanisms of action in idiopathic retroperitoneal fibrosis remain unknown.

As is the case of many immune-mediated diseases, idiopathic retroperitoneal fibrosis would also probably benefit from the combination of steroids and immunosuppressants. Mycophenolate mofetil and prednisone have been described in several small reports,[44,45] and in two larger series of 16[46] and 28 patients.[13] In the study of prednisone and micophenolate mofetil,[13] 25 patients (89%) had a 25% or higher reduction in size of retroperitoneal fibrosis, and ureteral stents were successfully removed in an equal number of patients; only two patients (7%) relapsed after treatment withdrawal. On the basis of these data and the low treatment-related toxic effects, mycophenolate mofetil plus prednisone will probably become a reference approach for idiopathic retroperitoneal fibrosis. Azathioprine has also been used with prednisone as first-line treatment in retrospective series (the largest of which included six to 15 patients);[14,15] the outcome of these cases was also good. The largest study assessing cyclophosphamide plus prednisone as first-line treatment included 11 patients;[14] of these, one died of pneumonia, one developed sepsis, and two severe leukopenia. Thus, the toxic effects of this approach are probably unacceptable. Methotrexate is also a feasible option, but the data for idiopathic retroperitoneal fibrosis are restricted to a few patients;[17] a randomised trial exploring the role of methotrexate as a steroid-sparing drug is currently underway at our centre (ClinicalTrials.gov number NCT01240850).

This study represents the first randomised controlled trial in idiopathic retroperitoneal fibrosis, and has a long patient follow-up period. It provides evidence that the treatment of this disease can be structured in a short induction phase of high-dose glucocorticoids and a subsequent maintenance phase with lower corticosteroid doses. The maintenance phase probably needs to be better explored, since steroid-sparing drugs might prove effective and safe in combination with prednisone. The study is, however, limited by its relatively small sample size and the absence of blinding, and by the fact that interventional procedures (eg, stent removal) were not protocolised a priori.

In conclusion, prednisone is better than tamoxifen in maintainance of remission in patients with idiopathic retroperitoneal fibrosis, and induces a greater shrinkage of the retroperitoneal mass than does tamoxifen. Despite the good outcome obtained with prednisone treatment, relapses are frequent, thus newer approaches are needed to achieve more sustained remissions and reduce steroid exposure.

Contributors

AV was involved in study design, enrolment and follow-up of patients, data collection, data analysis, and writing of the report. AP and FA were involved in enrolment and follow-up of patients, data collection, and analysis; UM was involved in data analysis and writing of the report. SF was involved in enrolment and follow-up of patients. RC and FF were involved in data collection and analysis (particularly in reviewing CT and MRI images). DC was involved in data collection and analysis (particularly in histological analysis). CS was involved in study design, enrolment of patients, and manuscript reviewing. CB was involved in study design, enrolment and follow-up of patients, data collection, and writing of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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