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Original Article

Long-term efficacy of hyperuricaemia treatment in renal transplant patients

Fernando Perez-Ruiz[1], Pablo Gomez-Ullate[1], Juan J. Amenabar[1], Sofía Zarraga[1], Marcelo Calabozo[1], Ana M. Herrero-Beites[2] and Joan M. Nolla[3]

[1]Hospital de Cruces, Rheumatology Section and Nephrology Division, Baracaldo, Pais Vasco, [2]Hospital de Gorliz, Rehabilitation Division, Gorliz, Pais Vasco and [3]Hospital Bellvitge, Rheumatology Division, Hospitalet, Barcelona, Spain

Abstract

Background. Although hyperuricaemia and gout are frequently found in renal transplant recipients, little has been published on the efficacy of urate-lowering therapy (ULT) in this patient population. We therefore examine the effects of allopurinol and benziodarone therapy in a cohort of renal transplant patients.

Methods. We reviewed files from a cohort of 1328 patients that received renal transplantation. The selection criteria included: functioning allograft, hyperuricaemia for >12 months or gout, ULT lasting at least 1 year and at least two control measurements after the onset of ULT. Patients on azathioprine were treated with benziodarone to avoid azathioprine–allopurinol interactions.

Results. Two-hundred and seventy-nine patients fulfilled the criteria for review. They were treated with 289 courses of ULT: 100 with allopurinol (mean dose: 376 mg/day/dl/min of creatinine clearance) and 189 with benziodarone (mean dose: 73 mg/day). The mean follow-up was 38 months. Both drugs were effective for the control of hyperuricaemia, but benziodarone caused greater reductions in serum uric acid levels, especially when used at mean doses of >75 mg/day. Severe side effects were uncommon, in both the allopurinol and benziodarone groups.

Conclusions. Both allopurinol and benziodarone were effective for the control of hyperuricaemia in renal transplantation. Benziodarone at doses $>$ 75 mg/day was more effective than allopurinol in reducing serum uric acid levels and also reduced the risk of azathioprine–allopurinol interactions.

Keywords: allopurinol; benziodarone; hyperuricaemia; renal transplant patients; serum uric acid; urate-lowering therapy

Correspondence and offprint requests to: Dr F. Perez-Ruiz, Hospital de Cruces, Rheumatology Section, Baracaldo, Pais Vasco, Spain. Email: fperez@hcru.osakidetza.net

Introduction

Hyperuricaemia and gout are frequently observed in renal transplant recipients [1–5]. Contributive factors to the development of hyperuricaemia include decreases in glomerular filtration rate and, especially, cyclosporin A (CSA) and diuretic therapies [3,4].

It is not clear whether hyperuricaemia itself or drug effects cause vascular events and reduced renal function in both transplant and non-transplant patients [6,7]. Urate-lowering therapy (ULT) in renal transplant patients may cause more adverse side effects than in the general population. For instance, renal function impairment may reduce the efficacy of probenecid or sulphinpyrazone [1] and concomitant azathioprine (AZA) therapy with allopurinol may increase the risk of developing severe bone marrow toxicity, despite the reductions in AZA dosage [8]. In addition, there is very little evidence on the efficacy of ULT in renal transplant patients and the few existing series include small numbers of patients and short follow-up periods [9–12]. We report herein the effects of ULT with allopurinol and benziodarone in a large cohort of renal transplant patients.

Subjects and methods

We reviewed files from a cohort of 1328 renal transplantation from 1979 to December 1998. These patients had been systematically treated with ULT after hyperuricaemia was observed during follow-up examinations. Patients on AZA therapy were given benziodarone in order to avoid allopurinol–AZA related toxicity.

The patients in the present study fulfilled the following criteria: functioning renal allograft—creatinine clearance (Ccr) >20 ml/min/1.73 m^2—at the time of the review, persistent hyperuricaemia lasting at least 12 months before ULT was initiated, except for patients with gout previous to transplantation or patients who developed gout in the first year after transplantation and ULT that lasted at least

12 months with at least two control measurements to evaluate efficacy.

We evaluated general characteristics of the patients, including age at transplantation, gender, diuretic prescription, immunosuppressive regimen, history of gout before transplantation, time from transplantation to the onset of hyperuricaemia or gout, urate-lowering drugs prescribed, mean doses of ULT during each year and during the entire follow-up period, doses corrected for Ccr (when allopurinol was prescribed), time of follow-up, number of analyses during follow-up, side effects attributed to ULT and withdrawal rate of ULT.

The blood and urine data were collected at baseline, during follow-up at 3, 6, 9, 12, 18, 24, 30, 36, 42 and 48 months and once every year thereafter. The baseline was designated the last analysis prior to the beginning of ULT. We measured serum uric acid (Sur) and creatinine (Scr) levels as well as urinary uric acid and creatinine in 24 h urine samples. Creatinine clearance and uric acid clearance (Cur) were calculated using standard formula and normalized for a body surface of 1.73 m^2. The fractional excretion of uric acid (FEur) was calculated as Cur/Ccr and was expressed as percentage.

Statistical analysis was performed using the EPI-INFO-2000 statistical package from the Centre for Disease Control, Atlanta, GA, USA. Data are expressed as means $\pm$ SD. Comparisons of continuous variables between groups were made using ANOVA. Analysis of paired variables (outcome at each control period during follow-up compared with baseline values) was made with paired *t*-tests. Comparisons between qualitative variables were made with chi-squared tests. *P*-values > 0.05 are expressed as non-significant (NS).

Results

From 1979 to 1998, 1328 renal transplantation procedures had been performed at our centre. From these procedures, 279 patients fulfilled the inclusion criteria and this patient group had been prescribed 289 courses of ULT: 100 with allopurinol and 189 with benziodarone. The analysis of follow-up after the fifth year was not reported due to a diminishing number of available patients.

The average age at transplantation was 43.7 $\pm$ 12.8 years (range: 9–70; median: 44) and 187/279 (67.3%) of the subjects were male. Age and gender were not different in the two ULT groups. Eleven patients (4%) had suffered gouty attacks before renal transplantation and 8 (3.2%) developed gout after transplantation. At the start of ULT, 76/289 (27.3%) patients were on diuretic therapy. Patients receiving immunosuppressive therapy (other than corticosteroids) included: CSA 100 (34.6%), AZA 5 (1.7%), combined CSA plus AZA 142 (49.1%), mycophenolate mofetil plus CSA 39 (13.5%) and tacrolimus 3 (1%). Thus, 281/289 (97.2%) courses of ULT were initiated while on CSA therapy.

Mean follow-up was 38.6 $\pm$ 18.4 months (range: 12–96). The mean number of controls registered during follow-up was 6.3 $\pm$ 2.8 (range: 2–14). Mean Ccr at the onset of ULT was 60.4 $\pm$ 23.7 ml/min/1.73 m^2, Cur was 3.27 $\pm$ 1.20 ml/min/1.73 m^2 and FEur was 6.17 $\pm$ 2.66%. There were no significant differences in these parameters at baseline between patients treated with allopurinol or benziodarone.

Although reductions in Sur in each control were different from baseline values during the first 2 years, there were no differences in Sur reduction during further follow-up, except when current benziodarone doses where compared with current benziodarone doses (Figure 1). Creatinine clearance did not change significantly compared with baseline in any group. Uric acid clearance and FEur were not altered in patients with allopurinol but had a 2–3-fold increase in patients treated with benziodarone (data not shown). The mean dose of allopurinol during the entire follow-up

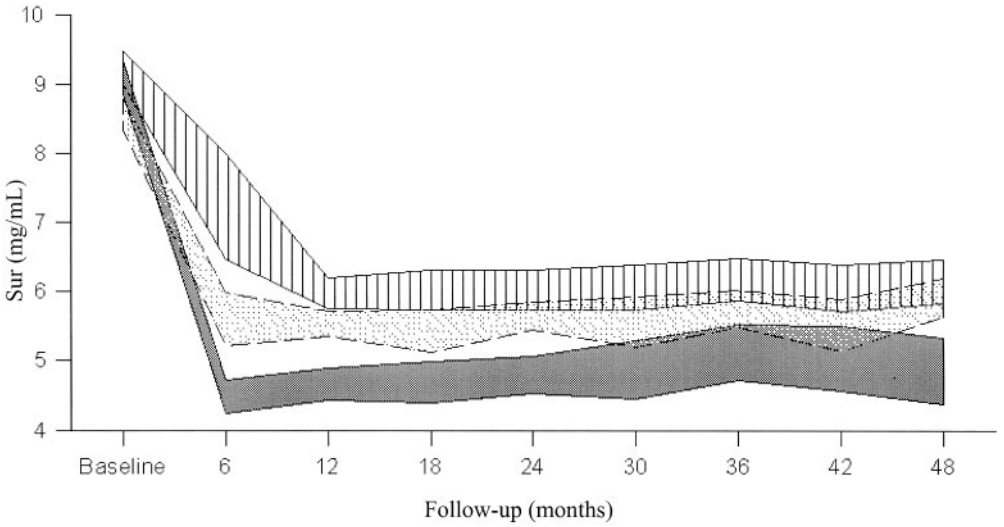

Fig. 1. Reduction of Sur including 95% confidence interval limits in patients on allopurinol (stripped area), benziodarone at a mean dosage of >75 mg/day (grey area) and benziodarone at lower doses (dotted area). Patients on benziodarone >75 mg/day achieved significant ($P<0.05$) reductions in Sur compared with the other groups during the entire follow-up.

was 185 ± 60 mg/day and was 376 ± 204 mg/day when corrected per dl/min of Ccr. The mean dose of benziodarone during the entire follow-up period was 73 ± 11 mg/day. The dosage of benziodarone significantly decreased during each year of therapy compared with that of the first year whereas the doses of allopurinol, corrected for Ccr, did not change significantly from the first to the fourth years of therapy.

In the allopurinol group, 11 patients were withdrawn because diuretic therapy was stopped and hyperuricaemia was not observed after diuretic discontinuation. In the 89 remaining patients, seven changed to benziodarone due to persistent poor control of hyperuricaemia and three due to severe side effects that included: one pancytopenia, one hepatitis (both patients were taking allopurinol > 600 mg/day/dl/min Ccr) and one patient with unexplained fever that subsided after allopurinol was discontinued. In the benziodarone group, withdrawal occurred because seven patients stopped ULT after diuretic withdrawal. In the 182 remaining patients, two patients suffered hypothyroidism due to the iodine content of benziodarone, four were changed to allopurinol due to lack of efficacy and 11 were stopped due to lack of efficacy but were not changed to allopurinol because they were still receiving AZA therapy. As a result, the withdrawal rates of allopurinol (10/89, 11%) and benziodarone (16/182, 8%) were not different from one another ($P = 0.672$).

Patients treated with benziodarone were analysed according to the mean dose prescribed during the entire follow-up period and in each year of follow-up. Patients that were treated with low doses showed lower baseline Sur levels, higher baseline Ccr and lower frequency of diuretic use than in patients with full benziodarone doses and also lower reduction of Sur compared to baseline than patients on current doses (Figure 1).

Discussion

Although hyperuricaemia is a frequent finding among renal transplant recipients and can occur in $\geqslant 90\%$ of patients treated with CSA and diuretics [4], gouty attacks are not that frequently observed, occurring in $\leqslant 12\%$ of patients on CSA [2]. The incidence of gout was low in our series and was less than in previous studies [2,5]. This was probably because patients were treated with ULT prior to the development of gouty symptoms.

There are three principal factors involved in the development of hyperuricaemia in renal transplant recipients: decreases in glomerular filtration and CSA and diuretic therapies. The reduction in glomerular filtration is probably not a major contributor to hyperuricaemia, except in patients with advanced renal insufficiency [1]. Results from some studies indicate that renal-transplant hyperuricaemia is mostly related to a reduction of tubular secretion of uric acid, especially in patients receiving CSA [12]. In our series, 97% of patients receiving ULT due to long-standing hyperuricaemia were on CSA therapy, either single or combined therapy. Diuretics are also known to contribute to hyperuricaemia in patients receiving CSA [2,4,5]. The course of diuretic therapy in our cohort was similar to that observed by others [2–5].

It remains unclear whether hyperuricaemia itself contributes to adverse vascular events and to the development of renal disease [6]. Recent findings suggest that uric acid levels are independently associated with cardiovascular events and are related to mortality [13] and on long-term transplant survival [14]. Recent experimental evidence supports the view that hyperuricaemia may aggravate chronic CSA nephropathy [7]. The mechanism does not involve uric acid crystal deposition, but appears to utilize activation of the renin–angiotensin system and inhibition of nitric oxide production, producing pathologic features that include arteriolar hyalinosis and tubular injury.

Reductions in Sur levels may be achieved using allopurinol, by reducing endogenous production of uric acid through inhibiting xanthine-oxidase activity or by using uricosuric drugs to enhance renal excretion of uric acid. Uricosuric drug action varies according to renal function, since a minimum load of uric acid must be present for uricosuric drugs to exert their action. Probenecid may be ineffective in patients on cyclosporin and both probenecid and sulphinpyrazone are less effective than allopurinol in patients with low glomerular filtration rate [1]. In addition, sulphinpyrazone reduces cyclosporin levels [15], placing patients at risk for rejection. Other measures may include changing cyclosporin to tacrolimus or to mycophenolate mofetil, which was recently shown not to interact with allopurinol [16]. Other uricosuric drugs that are available in the European Union, Japan, South Africa and some countries of the Americas, except for the United States, are the benzofurans, such as benziodarone and benzbromarone. They have been shown to be useful for the control of hyperuricaemia both in gouty patients with renal function impairment despite diuretic therapy [17] and in short-term studies with renal transplant patients on CSA [10–13].

In our series, both allopurinol and benziodarone were useful for the control of hyperuricaemia and the rate of side effects was low in both ULT groups. In addition, the side effects were within the known profile of adverse effects for both drugs [18]. However, the rate of side effects may have been biased since only patients with functioning allograft were reviewed. Furthermore, some side effects could have been caused to other therapies and mild side effects may have been overlooked in the patient's files.

Patients treated with benziodarone showed greater reductions in Sur than patients on allopurinol, especially when patients were treated with current benziodarone doses. A reduction in Sur from 35 to 50% was observed following 100 mg/day benziodarone or benzbromarone in renal transplant patients [9–13], with the poorest results observed in patients showing severe renal function impairment [11]. In our series, using

similar doses, both Sur reductions and FEur increases were similar to those reported by others [11,12].

The difference in efficacy between allopurinol and benziodarone probably may not be due to low allopurinol doses since the mean dose corrected for Ccr was > 300 mg/day/dl/min of Ccr [19,20]. In addition and when the dosage was similar to that used in primary gout [18], in gouty patients with moderate renal function impairment [17] or in renal transplant patients [10–13], there were clear-cut differences in the reduction of serum urate. This difference in dosage regimen may explain why no differences were observed in Sur reductions between groups after the first 2 years of therapy.

In conclusion, ULT may provide feasible treatment in patients with renal transplantation. Although both allopurinol and benziodarone are useful for treating hyperuricaemia in renal transplant recipients treated with CSA, full dose benziodarone seems to perform better than allopurinol.

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