Quinolone-related Achilles Tendinopathy in Heart Transplant Patients: Incidence and Risk Factors

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Background: A high incidence of Achilles tendinopathy—tendinitis or rupture—has been observed after quinolone treatment in lung and kidney transplant patients. In the absence of relevant published data, we aimed to determine its incidence, clinical features, risk factors and outcome among heart graft recipients.

Methods: We studied the clinical records of all adult heart transplant patients who were prescribed quinolones at our center between August 1995 and September 2006. Achilles tendinopathy had been diagnosed clinically, with ultrasound assessment when necessary. In all cases, quinolone treatment had been terminated upon diagnosis of tendinopathy.

Results: During this period, quinolones had been given on 242 occasions to 149 heart transplant patients (33 women, 116 men). Achilles tendinopathy developed on 14 occasions (5.8%; 95% confidence interval: 2.8% to 8.7%), affecting 13 men and 1 woman (mean age: 62 years). Three cases involved tendon rupture, and bilateral tendinopathy was present in 8 cases. The median time between the start of treatment and onset of symptoms was 2.5 days, with 12 patients being asymptomatic 2 months after drug withdrawal. Independent risk factors for tendinopathy were renal dysfunction ($p = 0.03$) and increased time between transplantation and treatment ($p = 0.005$). Incidence was not influenced by the type, dose or previous administration of quinolones, or by the immunosuppressive regimen.

Conclusions: Quinolone-related Achilles tendinopathy is frequent among heart transplant patients, especially in the presence of renal dysfunction or lengthy post-transplantation survival. If no alternative anti-bacterial therapy is available for high-risk patients, close clinical surveillance should be warranted. J Heart Lung Transplant 2008;27:46–51. Copyright © 2008 by the International Society for Heart and Lung Transplantation.

Because of their broad anti-bacterial spectrum and lack of interactions with immunosuppressive drugs, fluoroquinolones are frequently prescribed to heart transplant (HT) patients to treat common disorders such as gastroenteritis, tracheobronchitis and urinary tract infections. In general, these drugs are safe, and severe adverse effects are not frequent. In recent years, however, several case reports[1–4] and case–control studies[5–7] have related quinolones to a higher incidence of tendon disorders, mainly Achilles tendinitis and tendon rupture. Individual risk for this complication is low among healthy people, 0.14% to 0.40%,[8] but is increased by conditions such as old age, long-term corticosteroid therapy and kidney failure.[6,9] In particular, a very high incidence of quinolone-related Achilles tendinopathy (AT) has been reported among kidney[10] and lung[11] transplant patients, although for reasons not completely known. To the best of our knowledge, no studies have investigated whether the same is true among patients with heart grafts.

The aim of this study was to determine the incidence, clinical characteristics, risk factors and outcome of quinolone-related AT among HT patients.

METHODS

Study Description, Data Source and Variables

We conducted an observational historic-cohort–based study. We reviewed the clinical records of 519 consecutive patients who had undergone HT in the Heart

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Transplant Unit of our tertiary-level university hospital between April 1991 and September 2006 to identify all cases in which adults patients had been treated with ciprofloxacin, levofloxacin or norfloxacin between August 1, 1995 and September 30, 2006. To ensure quality and completeness of data, the study only included quinolone-exposure episodes from August 1995, the date when standardized collection of quinolone exposure and complications were incorporated into the follow-up protocol of heart transplant patients at our institution.

The raw data extracted, apart from demographic and transplantation data (gender, date of birth, date of HT, etc.), included: the quinolone administered; the infectious disease treated; administration route; daily quinolone dose; prior treatment with quinolones; dates of first and last quinolone dose; date of onset of symptoms of tendinopathy (if any); clinical characteristics of any AT; functional outcome 2 months after the withdrawal of quinolone; weight; serum concentrations of immunosuppressive drugs (cyclosporine, tacrolimus or mTOR inhibitor); daily dose of anti-proliferative drugs (azathioprine or mycophenolate mofetil); daily dose of prednisone; and serum creatinine level. The derived variables considered were: time between HT and quinolone treatment; age; body mass index (BMI); creatinine clearance; and cumulative quinolone dose. The latter variable was expressed as multiples of the defined daily dose (the average daily dose for an adult for the main condition treated),[12] which was 800 mg for norfloxacin, 1,000 mg for ciprofloxacin and 500 mg for levofloxacin.

Diagnosis of Tendinopathy and Follow-up

All patients prescribed quinolones were given instructions, at the time of prescription, about early signs and symptoms of tendinopathy. All inpatients were hospitalized in the Heart Transplant Unit, and a telephone was available to all outpatients and their general practitioners for the communication of any clinical events. All patients who reported symptoms suggestive of quinolone-related AT were examined by a physician in the Heart Transplant Unit. Tendinitis was diagnosed if the tendon was painful upon walking and palpation and showed signs of local inflammation[5] during the first 30 days after the first quinolone dose.[10] Tendon rupture was diagnosed if Thompson's test[9] was positive. In unclear cases, an ultrasound study was performed. Whenever tendinopathy was diagnosed, quinolone treatment was discontinued, rest was recommended, and the patient was given written instructions for physicians so as to prevent any subsequent prescription of quinolones. Conventional analgesic drugs such acetaminophen and metamizol were administered for symptomatic relief. For all patients who developed tendinopathy, data were obtained with regard to clinical status at 2 months after drug withdrawal.

Statistical Analyses

The chi-square and Fisher's exact tests were used for categorical variables, and the Mann–Whitney *U*-test for quantitative variables. As some patients were treated with quinolones more than once, and cases of AT also appeared in quinolone exposures other than the first (even when the patient had received quinolones previously without developing the complication), incidence analysis was based on "quinolone-exposure episodes" instead of "quinolone-treated patients." In the same way, because many clinical characteristics, such as age, creatinine clearance or time between transplantation and quinolone treatment, are different for the same patient at the moment of each exposure to the drug, analysis was also related to "quinolone-exposure episodes."

Risk factors for AT were investigated by multivariate logistic regression. In a first backward stepwise analysis that included age, gender, type of quinolone, cumulative quinolone dose, prior quinolone treatment, type of inmunossuppressive drug, steroid dose, significant kidney failure (creatinine clearance $<$60 ml/min) and time between transplantation and quinolone treatment, only these two last variables were independently associated with the risk of tendinopathy. Both remained in the final logistic regression model, together with selected variables—age, gender, levofloxacin treatment and steroid dose—that, although they did not reach statistical significance in our data, were suggested in the literature as potential risk factors for quinolone-related AT. The criterion for statistical significance was $p < 0.05$. All analyses were performed using SPSS, version 13.0.

RESULTS

Study Population

Between August 1995 and September 2006, quinolones were prescribed on 242 occasions to 149 HT patients at our center. Ninety-four of these patients were prescribed quinolones just once, 27 twice, 18 three times, 8 four times, 1 five times and 1 six times. The quinolone most often prescribed was levofloxacin (130 occasions), followed by ciprofloxacin (107) and norfloxacin (5). The most frequent administration route was oral (178 occasions), and the condition most frequently treated was a respiratory infection (125 occasions). Mean age at the time of quinolone treatment was 58.8 $\pm$ 10.6 years. Of the 149 treated patients, 33 were women (22.1%), who were prescribed quinolones on 51 occasions (21%).

Incidence and Outcome of Achilles Tendinopathy

Fourteen episodies of AT were diagnosed. None of the patients who developed AT were prescribed quinolones thereafter, so none suffered more than one episode of AT, and individual risk was 5.8% per exposure (95% confidence interval [CI]: 2.8% to 8.7%). Seven patients developed tendinopathy at their first quinolone exposure, four patients at the second, one patient at the third and two patients at the fourth. In 8 cases (57.1%) both Achilles tendons were affected, and rupture was diagnosed in 3 cases (21.4%). Diagnosis of AT was made solely on the basis of clear clinical signs in 10 cases, but in the other 4 (28.5%) it was necessary to perform an ultrasound study to obtain this diagnosis. The median time that elapsed between the first quinolone dose and the onset of symptoms was 2.5 days ($P_{75} - P_{25} = 3$ days). In 12 cases (85.7%), recovery was complete and the patient asymptomatic within 2 months of drug withdrawal. In the other 2 cases the patient remained symptomatic with chronic mild ankle pain upon walking. No patient needed surgical intervention, there were no permanent disabilities, and no relapses were detected.

Clinical Characteristics of Patients in Cases of Quinolone Exposure According to Development or Non-development of Achilles Tendinopathy

Significant renal dysfunction, defined as a creatinine clearance <60 ml/min, was significantly more frequent ($p = 0.02$) among cases of quinolone exposure in which a diagnosis of Achilles tendinopathy followed (85.7%) than in those where it did not (54.4%). A longer time since transplantation to quinolone therapy (4.4 ± 3.3 vs 2.4 ± 2.4 years, $p = 0.03$) was also observed among AT cases, but mean age was not significantly different between the two groups (61.7 ± 9.1 vs 58.6 ± 10.7 years, $p = 0.36$). Of the 14 episodies of AT, 13 were diagnosed in the men and only 1 in the women. This tendency, however, was not statistically significant ($p = 0.18$). No significant differences were found either with regard to prior exposure to quinolones (50% in the AT group vs 37.5% in the non-AT group, $p = 0.35$) or when other clinical characteristics were studied, as shown in Table 1.

Risk Factors for Achilles Tendinopathy: Multivariate Analysis

The only variables identified by multivariate logistic regression as independent significant risk factors for quinolone-related AT were a creatinine clearance <60 ml/min ($p = 0.03$) and increasing time between HT and quinolone treatment ($p = 0.005$). The risk of AT was not independently affected by dose of quinolone or prednisone, age, gender, the identity of the quinolone, prior quinolone treatment, or identity of the immunosuppressive drug used. The final regression model is shown in Table 2.

DISCUSSION

Over the past two decades, several investigators have reported that solid-organ recipients are particularly likely to develop tendon disorders after treatment with fluoroquinolones. In 1989, Murison et al observed what they regarded as a surprisingly high incidence (20%) of Achilles and supraspinatus tendinitis among a sample of 170 kidney transplant patients. At that time, association with fluoroquinolones was not suspected, but 5 years later Donck et al[11] reported a 12.2% incidence of Achilles tendinopathy in kidney transplant patients after quinolone treatment. More recently, Chhajed et al[10] found that, among 101 lung graft recipients, Achilles tendon disorders had developed in 22 (21.8%), 90% of whom had recently been treated with ciprofloxacin; the cumulative risk of AT after ciprofloxacin treatment was therefore 27.8% in that population. In our study, the individual risk of AT was 5.8% per exposure to quinolone. Although this figure is lower than reported for lung or kidney transplant patients, the difference may in part be due to the difference between risk per exposure and cumulative risk, because neither Chhajed nor Donck specified whether any of their patients had received quinolone treatment more than once. As such, our data confirm the suspicion that HT is a risk factor for quinolone-related AT, the incidence of which among HT patients was found to be >15 times the reported incidence among healthy people.[8]

The clinical characteristics of AT in this study were similar to those described by others. Bilateral involvement and tendon rupture were common, with frequencies consistent with those found by Van der Linden et al[3] and Khaliq and Zhanel.[4] Like these investigators, we observed that onset was usually acute, with most cases being diagnosed during the first week after the first dose of quinolone. The prognosis after withdrawal of the drug was good, with >80% of patients achieving complete recovery within 2 months. Similar recovery rates were observed in the Dutch study,[3] but other investigators have reported longer recovery times and higher rates of chronic sequelae such as pain, difficulty in walking or decreased flexion.[4] The low rate of long-term complications in the present study may have been influenced by the close clinical surveillance of our patients, allowing for earlier diagnosis of AT and withdrawal of quinolone.

The epidemiologic characteristics of AT in this study are also consistent with earlier reports. Van der Linden et al[5,6] found quinolone-related AT mainly among elderly patients and only very infrequently in young

Table 1. Clinical Characteristics of Heart Transplant Patients in 242 Cases of Quinolone Exposure According to the Development or Not of Achilles Tendinopathy

	Tendinopathy (n = 14)	No tendinopathy (n = 228)	p-value
Age (years)	61.7 ± 9.1	58.6 ± 10.7	0.36
Time since transplantation (years)	4.4 ± 3.3	2.4 ± 2.4	0.03
Gender			
Male	13 (92.8%)	178 (78.1%)	0.18
Female	1 (7.2%)	50 (21.9%)	
Infectious disease			
Respiratory infection	9 (64.3%)	116 (50.9%)	
Urinary infection	3 (21.4%)	46 (20.2%)	0.83
Gastroenteritis	2 (14.3%)	40 (17.5%)	
Other	0	25 (11.0%)	
Quinolone			
Levofloxacin	9 (64.3%)	121 (53.1%)	
Ciprofloxacin	5 (35.7%)	102 (44.7%)	0.65
Norfloxacin	0	5 (2.2%)	
Administration route			
Oral	10 (71.4%)	168 (74.6%)	0.76
Intravenous	4 (28.6%)	58 (25.4%)	
Prior quinolone treatment			
Yes	7 (50.0%)	86 (37.7%)	0.35
No	7 (50.0%)	142 (62.3%)	
Cumulative dose of quinolone (DDD)	9.0 ± 8.4	10.0 ± 10.4	0.56
Kidney function			
Creatinine clearance <60 ml/min	12 (85.7%)	124 (54.4%)	0.02
Creatinine clearance ≥60 ml/min	2 (14.3%)	104 (45.6%)	
Diabetes			
Yes	3 (21.4%)	63 (27.6%)	0.61
No	11 (78.6%)	165 (72.4%)	
Body mass index			
≥30 kg/m^2	5 (35.7%)	51 (22.4%)	0.32
<30 kg/m^2	9 (64.3%)	177 (77.6%)	
Immunosuppressive treatment			
Cyclosporine	10 (71.4%)	154 (67.8%)	
Tacrolimus	4 (28.6%)	61 (26.9%)	0.67
mTOR inhibitor	0	12	
Serum levels (ng/ml)			
Cyclosporine	175.6 ± 80.3	200.4 ± 98.1	0.44
Tacrolimus	11.7 ± 10.9	9.8 ± 3.9	0.47
Anti-proliferative treatment			
Azathioprine	10 (71.4%)	181 (79.4%)	
Mycophenolate mofetil	3 (21.4%)	23 (10.1%)	0.40
None	1 (7.1%)	24 (10.5%)	

DDD, defined daily dose (1,000 mg for ciprofloxacin, 500 mg for levofloxacin, 800 mg for norfloxacin).

patients, and in our study AT patients were, on average, >60 years of age. The fact that we found no statistically significant association between age and tendinopathy seems to be related to the range of ages in our sample being too narrow to provide sufficient statistical power. Similarly, the fact that the 13:1 (M:F) gender ratio in our AT patients was not statistically significant is probably attributable to the small proportion of women in our sample; other studies have also found AT to be more frequent among men.[3,10,14]

Little is known of the pathophysiologic mechanisms leading to quinolone-induced tendinopathy. Jorgensen et al[15] and Beuchar et al[16] suggested that an ischemic vascular process leading to tissue necrosis may cause the disorder, and LeHuec et al[17] indicated that it may be due to direct toxic insult to tendon collagen. In support of the latter hypothesis, quinolone has been found to induce oxidative stress involving altered proteoglycan anabolism and oxidation of collagen in the Achilles tendons of experimen-

Table 2. Risk Factors for Achilles Tendinopathy in Heart Transplant Patients: Results of Multivariate Logistic Regression Analysis

Variable	OR (95% CI)	*p*-value
Age (years)	0.99 (0.94–1.06)	0.90
Male gender	7.48 (0.81–68.91)	0.08
Creatinine clearance <60 ml/min	6.14 (1.23–30.64)	0.03
Time from transplantation to treatment (years)	1.39 (1.11–1.74)	0.005
Daily prednisone dose (mg)	1.02 (0.97–1.08)	0.43
Levofloxacin	1.37 (0.41–4.58)	0.61

OR, odds ratio; 95% CI, 95% confidence interval.

tal models.[18-20] It has also been hypothesized that tendon injury may result from the ability of quinolones to chelate polyvalent cations such as magnesium, and that correction of magnesium deficiency might have a protective effect.[21]

Chhajed et al[10] noted that tendinopathy seemed to be an idiosyncratic side effect of quinolone therapy rather than a dose-dependent consequence. In our study, risk was independent of dose, and was not increased by prior quinolone treatment if the prior treatment had not led to AT. We did not observe differences in AT incidence among the three quinolones used, although other investigators have reported a higher risk with perfloxacin[4] and levofloxacin.[22]

Several factors may contribute to the high risk of quinolone-related AT among HT patients. First, these patients are usually on long-term corticosteroid therapy, which is itself strongly associated with AT[5,6]; it has been reported that >50% of patients seen for Achilles tendon rupture were taking steroids.[4] It has been known for >30 years that corticosteroids delay the maturation of fibroblasts[23] and reduce the tensile strength of the tendon,[24] and these are the likely reasons why spontaneous repair of quinolone-induced tendon lesions is more difficult in patients undergoing steroid therapy.[20] In our cohort, all patients were taking prednisone, with the dose depending on the time that had elapsed since HT and on the patient's allograft rejection history. We found no statistically significant association between daily prednisone dose and tendinopathy, and the relationship with long-term cumulative steroid dose reported by Murison et al[13] has not been corroborated by other investigators[10]; however, a long-term relationship of this kind would certainly be in keeping with our finding that the risk of AT after quinolone therapy increases with post-transplantation time.

No association between AT and immunosuppressive drugs other than steroids has been reported, and it is not known whether the risk of AT for transplant patients could be enhanced by interactions between these drugs and fluoroquinolones or steroids. In our study, the risk of AT was not significantly influenced by the identity, dose or serum levels of the immunosuppressive drugs used at the time of quinolone treatment. It is worth noting that no cases of AT were diagnosed among patients on mTOR inhibitor therapy, but this observation must be evaluated with caution in view of the small number of such patients, namely 12.

Advanced kidney failure, especially in patients with end-stage kidney disease on long-term hemodialysis,[25,26] has also been associated with a higher incidence of spontaneous and drug-related tendon disorders, as has kidney transplantation.[11,13] The mechanism in these cases probably involves chronic acidosis,[27] which leads to the degeneration of tendons and changes in their tensile properties, and decreased clearance of quinolone,[8] which increases its toxicity. Chronic kidney failure is common among HT patients,[28] mainly because of the nephrotoxicity of immunosuppressive drugs. In our study, patients with a creatinine clearance of <60 ml/min were at significantly greater risk of quinolone-related AT. Furthermore, only two patients with normal kidney function (creatinine clearance >90 ml/min) developed AT. Kidney failure thus seems to be a major contributor to the high risk of quinolone-related AT among heart transplant patients.

The main formal limitations of our study are its observational, non-randomized design and the possibility of a certain degree of selection and information bias. It is possible that some patients may have been treated with quinolones by outside physicians, and that this information was not included in the Heart Transplant Unit's clinical records. It is also possible that some of the patients studied may, after quinolone therapy, have developed mild transient symptoms of AT without AT having been diagnosed. The former failing would result in overestimation of risk, and the latter in underestimation, but it seems unlikely that either circumstance would have involved a sufficient number of patients to alter our conclusions. For each patient who undergoes HT at our hospital, the Heart Transplant Unit maintains an individual dossier in which all relevant clinical information since the date of HT is prospectively recorded and periodically actualized. Moreover, patients and their general practitioners are encouraged to have knowledge of every clinical event, including new symptoms, complementary test results, changes of treatment and admissions to the hospital for any reason. A limitation that is probably more serious is the small number of occurrences of AT in this study, which undoubtedly limits its power to identify risk factors for AT. It seems likely that further risk factors, in addition to kidney failure and time since transplant, will emerge from larger studies.

In conclusion, the results of this study confirm that tendon disorders after quinolone therapy are common among HT patients. Although further studies are neces-

sary to gain a better understanding of the physiopathologic mechanisms and predisposing factors, quinolones should be avoided as much as possible in HT recipients whose clinical profile suggests a higher risk of tendinopathy— especially in male patients on long-term steroid therapy, with significant renal dysfunction, and when a long time has elapsed since transplantation. In this setting, other anti-bacterial drugs should be recommended as first-choice therapy depending on the type of infection and the clinical characteristics of the patient. If no alternative therapy is available, close clinical monitoring for early signs and symptoms of tendinopathy after quinolone prescription should be warranted to ensure prompt withdrawal of the drug, a higher probability of complete recovery, and a lower risk of long-term sequelae.

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