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The use of allopurinol in the inhibition of obliterative bronchiolitis of the transplanted lung

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Abstract. Long-term survival following lung transplantation has been limited primarily by the development in patients' lungs of a rejection-related obliteration of terminal bronchioles by fibroblasts. It is known to result from frequent and persistent acute lung rejection and its physiological features include a progressive decline in the lung function measurement of forced expiratory volume in 1 s. We report the dramatic effect on this hitherto usually fatal condition of a specific inhibition of purine metabolism at the xanthine oxidase enzyme by the hypoxanthine analogue allopurinol. The effect of this drug in heart-lung transplant patients with deteriorating lung function in reducing the rate of rejection and in stabilizing lung function was apparent over as short a follow-up period as 3 months and in ten patients. Although the follow-up time is short, we believe the effects are so striking as to require reporting although the mechanisms of this phenomenon are not yet well understood.

Key words: Xanthine oxidase – Allopurinol – Lung transplantation – Obliterative bronchiolitis – Rejection

Since the commencement of successful clinical trials of heart-lung transplantation, long-term survival has not been possible as a direct result of obliteration of small airways by fibrous tissue [obliterative bronchiolitis (OB)] [2]. International registry figures indicate survival as poor as 58% at 2 years [12].

Frequent, persistent and severe acute pulmonary rejection, are the major confirmed risk factors for the development of OB [16]. The frequencies of both acute and persistent acute lung rejection are related to progressive decline in the patients' baseline forced expiratory volume in 1 s (FEV_1), which is in turn characteristic of OB [16].

Pathologically, OB is characterized by progresssive destructive occlusion of small airways from a variety of causes [15, 17]. In lung transplant recipients occlusion of small pulmonary blood vessels may also occur [6, 7]. Fibroblast proliferation in small airways is probably triggered by local immunological injury in parallel with the parenchymal perivascular immature lymphocytic infiltrates described as occurring during pulmonary rejection [3, 6, 7]. The findings of open-lung biopsies and of post-mortem studies suggest that the often abrupt fall in FEV_1 characteristic of OB is associated with critical occlusion of numerous small airways by fibrous tissue [16, 17]. At our institute, only four of our first 14 patients survived 1 year following the development of OB.

The role of oxygen free radicals (OFR) in the genesis of lung injury and of fibrosis has previously been reported [5]. The production of OFRs is from several cellular sources, including xanthine-oxidase-catalysed reduction of hypoxanthine or xanthine. The potent stimulation by OFR of fibroblast proliferation has recently been described [14].

Allopurinol, a xanthine oxidase inhibitor, has been used in transplant organ preservation as has mannitol and other drugs with OFR scavenging properties [1, 9, 11]. Allopurinol has slight toxicity by itself, but has a major interaction with the widely used immunosuppressant antimetabolite azathioprine.

Table 1. Azathioprine (Aza) dosage (mg/day), cyclosporin (CyA) dosage (mg/day), whole blood monoclonal radioimmune assay of CyA levels (ng/ml), prednisolone (P) dosage (mg/day) and patient weight (kg), prior to therapy with allopurinol

Patient	Aza dose	CyA dose	CyA level	P dose	Weight
1	25	350	281	0	62
2	12.5	325	230	0	55
3	37.5	1175	113	0	56
4	75	150	152	10	50
5	100	400	403	5	74
6	175	900	41	10	57
7	25	225	93	2.5	52
8	25	325	334	10	57
9	150	325	1028	15	63
10	50	1425	325	15	50

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Table 2. Number of acute lung rejection (R) and infection (I) episodes in the 3 months prior to commencing allopurinol

Patient	R episodes	I episodes
1	2	0
2	0	0
3	0	1
4	6	0
5	4	1
6	4	0
7	1	0
8	2	1
9	2	0
10	2	0

Table 3. Mean change in percent predicted forced expiratory volume in one second (FEV_1) in the 3 months before and in the 3 months after institution of therapy with allopurinol for each of the ten patients

Patient	Mean change in FEV_1 (% of predicted)	
	3 months before	3 months after
1	− 8.8	−5.0
2	− 5.0	0.0
3	− 3.1	+3.1
4	−30.9	+2.0
5	−28.5	+9.6
6	−25.6	0.0
7	−11.0	+7.3
8	− 5.3	+2.7
9	− 7.6	+2.0
10	−14.0	+3.5

Methods

Since April 1984, 101 patients have received HLT at our institute, of whom 66 were alive at the time of writing, 46 of whom more than 1 year after surgery. Of the 66 survivors, ten patients (six male, four female), of average age 32.6 years (range 21–47 years) and average time since transplantation of 982 days (range 267–1665 days), had an irreversible decline in FEV_1 over the 6 months prior to the commencement of this study. All patients were considered at high risk for the development of OB, with frequent and persistent episodes of treated acute lung rejection. Average FEV_1 prior to allopurinol therapy was 53.7% of predicted (range 20.9–91.2%).

These patients were therefore commenced on allopurinol 200–600 mg/day in order to achieve a serum urate less than 0.20 mmol/l. The azathioprine dosage was initially reduced to 25% of the previous dose.

Lung function, blood chemistry, haematology, and whole-blood monoclonal assays for cyclosporine were performed and immunosuppression dosage recorded on a regular basis before and after allopurinol therapy was commenced (Table 1). The frequency of infection and rejection episodes was also recorded (Table 2), as was the rate of hospital admissions.

Results

Mean white blood count in the 3 months prior to commencement of allopurinol was 6.1 (range 4.7–7.9) and was 6.0 (range 4.9–7.0) in 3 subsequent months (P = NS). There was also no significant difference in neutrophil count, lymphocyte count, haemoglobin, platelets, cyclosporine dose or levels, nor in oral steroid dosage. All but one patient had a stable or increased weight over the 3 months following commencement of the drug.

Mean change in FEV_1 over the 3 months prior to the introduction of allopurinol was −13.9% of predicted FEV_1 (+/− standard error 3.3). The mean change in FEV_1 in the next 3 months was +2.4% (+/− standard error 1.3). The difference between the mean change in FEV_1 before and after allopurinol was commenced was significant when analysed using the paired Student's t-test ($t = 4.26$; $P = 0.003$. Individual mean changes in FEV_1 are given in Table 3.

Rejection episodes averaged 2.4/patient per 3 months before and 0.3/patient per 3 months after commencement of treatment with allopurinol; using McNemar's test with continuity correction this difference was significant ($z = 2.5$; $P = 0.013$). The frequency of infection was comparable, averaging 1.6 episodes/patient per 3 months before and 1.5 episodes/patient per 3 months after allopurinol was started (P = NS).

Discussion

We have demonstrated the short-term effect of high-dose allopurinol in preventing further decline in FEV_1 towards disability and death which has plagued lung transplantation. This prospective study was not randomized, reflecting our level of clinical concern for these patients with deteriorating lung function. The mechanism of this effect is unknown, but the reduction in the frequency of rejection without an overall increase in the frequency of infection suggests its effect is not merely an enhancement in the overall level of immunosuppression.

Since under conditions of ischaemia, and perhaps under those of inflammation, inhibition of xanthine oxidase may result in a reduction in OFR generation [10] and OFR have been implicated in the genesis of fibroblast proliferation [14], it is possible that allopurinol has had this striking effect by way of OFR inhibition [8]. The alternative hypothesis is that the interaction of allopurinol and azathioprine results in a change in the profile of active azathioprine metabolites [4], including 6-mercaptopurine, and this results in an enhancement of anti-inflammatory and/or immunosuppressive activity. Some support for this second hypothesis can be argued from the report of the attenuated decline in FEV_1 in HLT patients following the initial introduction of azathioprine at Stanford [6].

The OFR hypothesis can be assessed by measurement of secondary products of OFR, such as lipid hydroperoxide [13] and the alternative hypothesis can be examined by study of azathioprine metabolites [4].

These results should be cautiously interpreted, since this was not a randomized study and accordingly we have now undertaken a prospectively randomized study in recent HLT recipients prior to initial hospital discharge. The long-term effects are not yet known. However, if further studies confirm this observation, the implications for lung transplantation are potentially profound. The internationally reported prospects of 58% survival at 2 years after undergoing the established combined heart and lung

transplant procedure [12] could be significantly improved. The dramatic fall in acute lung rejection without apparent change in the level of immunosuppression, and with no increase in the level of infection, suggests that this approach may well have wider application in the general transplant field. We are aware of the short follow up in these patients, but believe that the possible implications of this preliminary study require us to report these observations for comment and criticism.

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