Phase I and Pharmacokinetic Study of Flavone Acetic Acid

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ABSTRACT

Flavone acetic acid is the second in a series of compounds based on the flavonoid aglycone ring structure to be clinically evaluated in malignant disease.

Preclinical studies have indicated that a minimum plasma level of 150 μg/ml is required before therapeutic efficacy (in a wide range of experimental tumors) is seen in mice; both in vitro and in vivo studies also suggest that the duration of drug exposure is crucial in determining activity. Thus a Phase I trial has been performed in a total of 54 patients using 3 schedules, i.e., a 1-, 3-, and 6-h infusion. In each case, treatment was given once weekly for a minimum of 3 weeks. The maximum tolerated doses were 6.4, 6.4, and 10.0 g/m², respectively. Dose limiting toxicity was denoted by an intense feeling of warmth and flushing with a 1-h infusion, hypotension with a 3-h infusion, and hypotension and diarrhea with a 6-h infusion. No objective responses were seen in this Phase I trial.

The recommended doses for Phase II trials of flavone acetic acid in Europe are 4.8 g/m² over 1 h or 8.6 g/m² over 6 h. At these doses the peak plasma concentrations obtained are 650 and 388 μg/ml, respectively. Total drug exposure (assessed by an area under the curve > 100 μg/ml) was approximately 50% greater for the 6-h schedule.

This Phase I trial indicates that peak plasma concentrations associated with experimental activity are achievable in humans, although optimal drug exposure times have not yet been defined.

INTRODUCTION

FAA is the second of a series of compounds based on the flavonoid aglycone ring structure to undergo clinical evaluation in malignant disease (Fig. 1). The parent compound (flavone acetic acid ester; LM985) was not recommended for Phase II assessment because of drug associated acute hypotension and the fact that it appeared to function as a prodrug with rapid hydrolysis in vivo to FAA (1).

Preclinical studies with FAA indicate that it is active against a broad spectrum of murine transplantable solid tumors which tend, on the whole, to be refractory to conventional cytotoxic agents, including a range of colon adenocarcinomas, pancreatic ductal adenocarcinoma, mammary adenocarcinoma, and Glasgow's osteosarcoma (2, 3). In addition, a soft agar colony formation assay, against mouse transplantable colon tumors (MAC cell line) has been shown to depend on the length of exposure as well as drug concentration (5). Therefore both the plasma concentration achieved and the duration of exposure above a critical limit are important determinants of toxicity and possibly efficacy.

We report here a Phase I and clinical pharmacokinetic study of this compound, following administration by three different schedules (1-, 3-, and 6-h infusions). This was facilitated by drug supply from Lipha Lyonnaise Industrielle through the National Cancer Institute liaison office in Brussels.

MATERIALS AND METHODS

Patient Selection. Patients with histologically confirmed metastatic cancer refractory to conventional treatment were entered into the study, after fully informed consent had been obtained. Eligibility criteria included adequate performance status (WHO grade 0–2), adequate pretreatment bone marrow (WBC > 3 x 10⁹; platelets > 100 x 10⁹), and hepatic (bilirubin < 20 μmol/l) and renal (creatinine < 120 μmol/l) function.

Fifty-four patients were entered into the study and their characteristics are summarized in Table 1. Pretreatment evaluation included complete physical examination, chest radiograph, 12-lead electrocardiogram, urinalysis, and measurement of standard hematological and biochemical parameters. In addition measurements of evaluable disease were made including ultrasound examinations, computer assisted tomography, and isotope scans as appropriate. During therapy, patients were under constant observation and pulse and blood pressure were measured every 15 min. During treatment the patients attended for weekly examination and repeat estimation of hematological and biochemical parameters. Evaluation of tumor response was performed with repeat physical examination, conventional radiology, and scans at approximately 6-weekly intervals.

Drug Administration. FAA was provided by LIPHA, Lyonnaise Industrielle. It was supplied in sterile vials as a freeze-dried powder (1 g/vial) which was reconstituted in 10 ml of sterile water. The drug was diluted in 0.5–1 liter of 0.9% saline and infused at a constant rate over 1, 3, or 6 h. Treatment was repeated weekly for 3 courses, and if there was no evidence of disease progression a further 3 courses were administered at weekly intervals. The drug was infused initially over 1 h with a starting dose of 0.5 g/m² and was escalated thereafter according to a modified Fibonacci scale (from 2 to 4 patients were treated at each dose level). Within patient dose escalation was not permitted until the latter stages of the study when it was clear that cumulative toxicity did not occur. However, patients were escalated to a higher dose only after 2 new patients had received the higher dose. After dose limiting toxicity had been reached for a 1-h infusion, the drug was infused over 3 and then 6 h from a starting dose of 4.8 g/m². Dose escalation was stopped when at least 50% of patients entered at that dose had experienced significant side effects which were considered dose limiting. Individual patients received more than 6 courses if there was no evidence of progressive disease in the absence of toxicity. FAA is relatively insoluble at neutral and acid pH values. This could result in potential nephrotoxic effects due to the high concentrations (>100 μg/ml) required for activity and that animal lethality could result from two causes. Acute lethality was associated with high peak plasma concentrations (>600 μg/ml). Delayed death could result from prolonged exposure at plasma concentrations within the therapeutic window (100–600 μg/ml). The antitumor activity of FAA, assessed by an in vitro colony forming assay, against mouse transplantable colon tumors (MAC cell line) has been shown to depend on the length of exposure as well as drug concentration (5). Therefore both the plasma concentration achieved and the duration of exposure above a critical limit are important determinants of toxicity and possibly efficacy.

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1 We thank the Cancer Research Campaign and the Investigational Drug Branch, Cancer Therapy Evaluation Program, National Cancer Institute, under whose auspices this study was performed.

2 To whom requests for reprints should be addressed.

3 On behalf of the Phase I Committee of the Cancer Research Campaign and the Early Clinical Trials Group of the European Organization for Research on Treatment of Cancer.

4 The abbreviations used are: FAA, flavone acetic acid; AUC, area under the concentration-time curve.

5 H. Fiebig, personal communication.
bicarbonate over 1 h before and after all infusions of FAA. In order to circumvent this problem we infused 500 ml of 1.26% sodium bicarbonate before and 24 h). Each sample was centrifuged immediately (2000 rpm for 5 min) and the plasma was frozen and stored at -20°C until assayed.

Blood was collected into heparinized tubes during the infusion and up to 24 h after administration of the drug (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h). Each sample was centrifuged immediately (2000 rpm for 5 min) and the plasma was frozen and stored at -20°C until assayed. Urine was collected for 24 h following drug administration in 14 patients, over the dose range 0.5-3.6 g/m² by 1-h infusion.

Clinical Pharmacological Studies. A pharmacokinetic study was performed on each patient at entry into the trial at all dose levels. Blood was collected into heparinized tubes during the infusion and up to 24 h after administration of the drug (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h). Each sample was centrifuged immediately (2000 rpm for 5 min) and the plasma was frozen and stored at -20°C until assayed. Urine was collected for 24 h following drug administration in 14 patients, over the dose range 0.5-3.6 g/m² by 1-h infusion.

Drug Analysis. A high performance liquid chromatographic assay was devised using p-dimethylaminobenzaldehyde (BDH Chemicals, England) as internal standard. The mobile phase was composed of 12.5% methanol, 12.5% isopropyl alcohol, 12.5% acetonitrile, and 62.5% 0.005 M phosphoric acid.

The extraction of FAA involved the addition of 0.1 MB of internal standard to 1 ml of plasma. After vortexing, 200 µl of 5% trichloroacetic acid were added followed by 10 ml of chloroform. Each sample was then vortexed at room temperature for 1 h; the precipitate and aqueous phase were then sedimented by centrifugation for 15 min at 2000 rpm. The drug containing organic layer was then removed and evaporated at ambient temperature using a Buchler vortex evaporator. The residue was redissolved in 200 µl of methanol. The extraction efficiency of FAA was approximately 75% and the internal standard was 80%.

The high pressure liquid chromatograph (Model Altex 100 A; Altex Scientific, Inc., Berkeley, CA) contained a single constant flow pump which delivered a flow rate of 1.5 ml/min. The stainless steel column (250- x 5-mm inside diameter) was packed with (5 µm) C₁₈-Bondapak.

Table 1 Summary of patient characteristics in the study

<table>
<thead>
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<th>No. of patients entered</th>
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<tr>
<td>Median age (yr) and range</td>
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<tr>
<td>Sex (M:F)</td>
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<tr>
<td>Median performance status (WHO) median</td>
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Pathological diagnosis

| Colorectal | 17 |
| Adenocarcinoma of unknown primary | 15 |
| Kidney | 5 |
| Stomach | 4 |
| Cervix | 1 |
| Ovary | 6 |
| Other | 6 |

Prior therapy for advanced disease

| Surgery | 34 |
| Radiotherapy | 10 |
| Chemotherapy | 20 |
| Hormones | 2 |
| Nil | 5 |

Sites of metastasis

| Liver | 20 |
| Lungs | 17 |
| Lymph nodes | 12 |
| Bone | 3 |
| Other | 8 |

Samples were injected onto the column via a manual injection port containing a 20-µl loop (Altex 210). The eluant was freshly prepared and degassed daily. A variable wavelength UV detector (LC-UV Pyc; Unicam, England) was set at 303 nm and 0.02 absorbance unit full scale to detect the eluting compounds. The output signal was recorded by a Tekman potentiometric pen recorder. All separations were performed at ambient temperature using isocratic elution. A standard curve was prepared by plotting the ratio of peak heights of FAA to internal standard against the drug concentration. The curve was linear in the range 10-1000 µg/ml. Urinary drug concentration was assayed by direct injection of 20 µl of urine onto the column, as described previously. The assay was sensitive to a drug concentration of 1 µg/ml, the lowest reliable peak height taken as three times greater than the height of base line noise. FAA and the internal standard chromatographed as single peaks with respective retention times of 12.5 and 7.5 min. Interassay and intraassay coefficients of variation are 10 and 8%, respectively.

Pharmacokinetic Calculations. The area under the plasma concentration-time curve was calculated using the log trapezoidal rule, from time 0 to the last measured time point and then extrapolated from the last time point to infinity. The terminal half-lives were found by calculating the significance of the regression using the determination coefficient by the least squares method. Both two and three compartment open models corrected with appropriate infusion models were evaluated for “goodness of fit” to the patient plasma concentration-time data at all dose levels. Each patient data set was fitted by nonlinear least squares using an “in house” program based on the Marquandt algorithm (6). The best fits were obtained using a two compartment open model and 1/τ² as a weighting term. It was possible to calculate the drug clearance and steady state volume of distribution from the microscopic rate constants. Although the drug has nonlinear pharmacokinetics, the linear models used to fit the data approximated well. However, nonlinear modeling using the ADAPT program has been undertaken by A. Gouyette.

RESULTS

Fifty-four patients were entered into the study and they were all considered evaluable for assessment of toxicity. A total of 208 courses of the drug were administered, with doses ranging from 0.5 to 10 g/m². The number of patients entered and concentration given at each dose level are summarized in Table 2.

Toxic Effects of FAA

All Schedules. The major toxic effects noted during this Phase 1 study were associated with drug administration, i.e., occurred during drug infusion. At subsequent assessments, i.e., at weekly intervals before treatment, there was no evidence of any hematological (i.e., WBC > 3 x 10⁹; platelets > 100 x 10⁹) or biochemical disturbance attributable to the drug with one exception described below (Table 3). There was some nausea and vomiting at doses greater than 3.6 g/m² for all infusions. However, this was not protracted and responded to conventional antiemetics. Most patients noted muscular aches associated with some stiffness, usually affecting the thighs and shoulder girdle, at doses greater than 4.8 g/m². This persisted for approximately 24 h after it resolved spontaneously. Serum creatine phosphokinase was measured before drug infusion and 24 h after therapy in 25 patients (dose range, 0.5-6.4 g/m² over 1 hr). A significant rise in the skeletal muscle isoenzyme (2-10 times the upper limit of normal) was seen in 4 subjects. The degree of muscular pain and stiffness did not correlate with the 24-h serum creatine phosphokinase concentration in the majority of patients.

One-Hour Infusion. There was a feeling of warmth and flush-
ing at all doses greater than 2.7 g/m². This was dose related and dose limiting at 6.4 g/m² over 1 h. Both patients receiving this dose complained of an intolerable sensation of warmth and flushing which was associated with profuse sweating. Recordings of oral temperature were made in one patient with a standard clinical thermometer during and after the infusion. Oral temperature had fallen by approximately 2°C (from 36.8°C to 35°C) by the end of drug infusion but had returned to normal by 2 h postinfusion. Therefore, despite a distressing feeling of warmth, the patient was mildly hypothermic. At 3.6 g/m² over 1 h, one patient experienced a mild allergic reaction, consisting of a widespread urticarial rash, approximately 15 min after first exposure to the drug. This responded rapidly to i.v. administration of hydrocortisone and chlorpheniramine.

No other significant toxicity, in particular hypotension, was evident in this phase of the study.

After dose limiting toxicity had been reached for a 1-h infusion, patients were then entered at 4.8 g/m² over 3 h.

Three-Hour Infusion. Dose limiting toxicity was reached at 6.4 g/m² over 3 h when 2 of 4 patients entered became hypotensive near the end of the infusion. Blood pressure fell from a pretreatment mean of 124/78 mm Hg to 70/50 mm Hg. The hypotension was symptomatic and the patients felt lightheaded and dizzy and noticed increased perspiration. The drug infusion was terminated, plasma volume expanders were infused, and hypotension was symptomatic and the patients felt lightheaded and dizzy and noticed increased perspiration. The drug infusion was terminated, plasma volume expanders were infused, and the blood pressure fell from a pretreatment mean of 124/78 mm Hg to 70/50 mm Hg. The hypotension was symptomatic and the patients felt lightheaded and dizzy and noticed increased perspiration. The drug infusion was terminated, plasma volume expanders were infused, and the blood pressure fell from a pretreatment mean of 124/78 mm Hg to 70/50 mm Hg. The hypotension was symptomatic and the patients felt lightheaded and dizzy and noticed increased perspiration. The drug infusion was terminated, plasma volume expanders were infused, and the blood pressure fell from a pretreatment mean of 124/78 mm Hg to 70/50 mm Hg. The hypotension was symptomatic and the patients felt lightheaded and dizzy and noticed increased perspiration.

Six-Hour Infusion. FAA infusions were commenced at 4.8 g/m² and escalated to 10 g/m², at which point dose limiting toxicity in the form of severe watery diarrhea and hypotension was noted. Nausea and vomiting was more marked during the 6-h infusion but generally lasted for only 1–2 h after the end of the infusion and responded to conventional antiemetics. Thirty of 14 patients had mild, asymptomatic hypotension during infusion of 8.6 g/m² with a fall in systolic blood pressure of 20–30 mm Hg. Drug infusion was discontinued and the blood pressure rose gradually over the next 2–4 h. At 10 g/m², severe watery diarrhea necessitating a dose reduction in 1 patient was noted. The diarrhea persisted for 12 h and the patient passed 12–14 watery stools during this period. No treatment was required after 24 h and no electrolyte disturbances were noted.

There was a fall in systolic blood pressure (35–40 mm Hg) in 2 patients in midinfusion which required cessation of therapy. One of these patients developed marked sedation in association with the hypotension. In addition, one male patient (44 years) with an adenocarcinoma of unknown primary origin, with no objective hepatic involvement (abdominal ultrasound) developed cholestatic jaundice 1 week after his ninth dose of FAA (8.6 g/m²). This was characterized clinically by generalized itching and the passage of pale stools and dark urine and biochemically by a raised bilirubin (100 µM; normal range, 3–18 µM), alkaline phosphatase (360 units/liter; normal range, 90–210 units/liter), and normal hepatic transaminases. There was no evidence of extrahepatic biliary obstruction (abdominal ultrasound, endoscopic retrograde cholecystopancreatography).

Liver biopsy was consistent with mild cholestatic jaundice and other investigations including viral antibodies were negative. At the point of developing cholestasis the patient had been treated with 9 courses of FAA (10 g/m² for 3 treatments plus 8.6 g/m² for 6 treatments), i.e., a total dose of 81.6 g/m². However, he had also received with his 8th and 9th doses the phenothiazine, prochlorperazine, which is known to be associated with cholestatic jaundice. With his last course of FAA he had received a total of 37.5 mg of prochlorperazine because vomiting was more marked. Treatment with FAA was halted, and the patient was given no further prochlorperazine. The cholestatic jaundice slowly improved over the ensuing 4 weeks. One other patient has received a total dose over 9 courses of 85.8 g/m² without signs of drug induced cholestasis.

Therapeutic Response

Forty patients had measurable disease and were evaluated for response. However, no responses were observed according to WHO criteria.

Pharmacokinetic Studies

The mean pharmacokinetic parameters for the patient group are summarized in Table 2. It is apparent that the pharmacokinetic parameters show dose dependent behavior. This is represented graphically in Fig. 2, in a plot of AUC for individual patients versus dose, where a curvilinear relationship is seen for dose and exposure to the drug. This responded rapidly to i.v. administration of hydrocortisone and chlorpheniramine.

Table 2 Mean pharmacokinetic parameters for each dose level

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<th>Duration of infusion (h)</th>
<th>No. of patients entered</th>
<th>Dose level (g/m²)</th>
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<th>Clearance (liters/h/m²)</th>
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* Includes patients also treated at 7.5 and 10.0 g/m².
Fig. 2. Relationship between area under the concentration-time curve and dose for 1-h infusions. •, single patient.

The observed peak plasma concentrations was seen as dose was escalated. However, it is interesting to note that at the higher doses on the 6-h infusion, clearance is not very dose dependent. This could reflect reduced plasma concentrations following prolongation of the duration of infusion.

The mean steady state volume of distribution tended to decrease as dose increased (Table 2). This was due to diminution in size of the peripheral compartment \( V_2 \) because the central compartment \( V_1 \) was found, generally, to remain the same size (data not shown).

The amount of drug excreted in the urine in 24 h following treatment was expressed as the percentage of the total dose recovered in the urine (mean, 25%; range, 4–44%). There was no apparent association between drug dose and urinary excretion. Two urinary metabolite peaks have been noted on high performance liquid chromatographic analysis of patient urine samples and await purification and identification, but preliminary assessment concludes that the metabolites can contribute up to 60% of total urinary drug concentration. The flavonoid aglycones, as a group, do tend to be metabolized by hepatic glucuronidation (7), and it is possible that the urinary metabolite peaks are glucuronides.

The therapeutic window described in mice of 100–600 \( \mu \)g/ml is clinically achievable in humans at the recommended doses for each infusion rate. It appeared subjectively that the degree of flushing and warmth reported by individual patients correlated with the end of infusion peak plasma drug concentration;
however, there was no obvious pharmacokinetic rationale to explain the hypotension noted at 3- and 6-h infusions. In view of the suggestion that toxicity could be related to the duration of exposure above plasma threshold concentration, as well as the peak plasma level achieved, we explored the concept that the AUC above an arbitrary plasma concentration of 100 μg/ml (cf, murine data) could be an important determinant of both toxicity and efficacy.

Table 4 summarizes the AUC (>100 μg/ml) and end of infusion peaks for 1-, 3-, and 6-h infusions at doses >4.8 g/m². The mean plasma concentration-time curves for 1-h (4.8 g/m²) and 6-h (8.6 g/m²) infusions are shown in Fig. 3. If the AUC concept is correct, then drug delivery by a 6-h infusion could be more efficacious. There did appear to be a correlation between the peak plasma level achieved and the degree of subjective warmth and flushing, but not with the other major types of toxicity seen. A possible pharmacological explanation for the different type of toxicity seen during the more prolonged drug infusion could be accounted for by the lower end of infusion peak plasma concentration, but higher AUC > 100 μg/ml.

DISCUSSION

Flavone acetic acid has entered clinical studies because of its unusually broad spectrum of experimental tumor activity, with only modest activity in the standard P388 and L1210 leukemia models. This implies a novel mechanism of action that remains to be defined. Some reports have demonstrated DNA strand breaks, but others have suggested that this is a secondary event. Since FAA does not act as a conventional cytotoxic agent, toxicity could be expected to be different from the usual and this was confirmed in preclinical studies and in this Phase I trial. Dose limiting toxicity in this Phase I study differed according to the schedule of drug administration. An intense feeling of warmth and flushing was found to be dose limiting according to the schedule of drug administration. An intense feeling of warmth and flushing was found to be dose limiting for 3- and 6-h infusions. It is interesting to note that acute hypotension was found to be dose limiting in the Phase I trial of FAA ester (LM985) previously carried out in our department (1). FAA ester appeared to be a prodrug undergoing protelolytic cleavage in plasma to FAA and diethylethanolamine, and murine studies showed that FAA (10 mg/kg i.v.) had no effect on blood pressure. The highest level of FAA achieved in plasma at the maximum tolerated dose for FAA ester was 26 μg/ml, far short of the therapeutic window suggested by the murine studies, and it was not recommended for Phase II trials.

FAA has dose dependent pharmacokinetics with a nonlinear relationship between dose and the AUC for the plasma concentration-time curve and end of infusion peak drug concentrations. The mean total body plasma clearance (CL) decreased as the dose was escalated, whereas the mean steady state volume of distribution (Vdss) tended to decrease with increasing dose. The decrease in Vdss was the result of decrease in the volume of the peripheral compartment (V2), since the central compartment volume of distribution (V1) remained relatively unchanged (data not shown). Pharmacokinetic studies were carried out in a few patients at different dose levels and dose dependent pharmacokinetic behavior was also manifest within an individual patient. The dose dependent behavior of body plasma clearance and mean steady state volume of distribution implies a common saturable pathway. Rate limiting steps for both drug elimination and drug tissue binding within an organ of metabolism or excretion have been described (9) and could explain the rate saturating tissue uptake mechanism implied by the pharmacokinetic behavior of FAA. We are currently characterizing two major metabolites in urine and plasma and this will give further information on the possible dose dependency of hepatic or renal elimination. The pharmacokinetic results de-

<table>
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<th>Duration of infusion</th>
<th>1 h</th>
<th>3 h</th>
<th>6 h</th>
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<td>Dose (g/m²)</td>
<td>Peak (μg/ml)</td>
<td>AUC (Cp &gt; 100 μg/ml)</td>
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* Cp, plasma concentrations.
PHASE I TRIAL OF FLAVONE ACETIC ACID

Fig. 3. Mean plasma concentration-time curves for 4.8 g/m² by 1-h infusion (○) and 8.6 g/m² by 6-h infusion (□), the schedules recommended for Phase II trials.

scribed here are similar to those reported by Staubus et al. (10) from their Phase I trial of FAA.

The pharmacokinetic studies also demonstrate that the therapeutic window shown in mice is clinically achievable. However, there are numerous theoretical reasons why direct extrapolation from mice to humans may be misleading, including differences in drug metabolism and disposition and interspecies variation in plasma protein binding. Data on the latter point indicate that plasma protein binding in humans is saturable within the range of plasma levels achieved in this study and is approximately 4 times greater than in mice.

Caution is therefore warranted in interpretation of these pharmacological data, but further clinical evaluation of FAA is justified since it represents a novel structure possessing definite biological activity against experimental tumors. Phase II studies have commenced in Europe using 2 schedules, 4.8 g/m² by 1-h infusion and 8.6 g/m² by 6-h infusion.

The phase II studies will include patients with breast, colorectal, and renal carcinomas and melanoma.

ACKNOWLEDGMENTS

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REFERENCES


* J. Collins, personal communication.
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