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PHASE I STUDIES

Phase IB trial of oral talactoferrin in the treatment of patients with metastatic solid tumors

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Summary *Purpose*: We evaluated safety and activity of talactoferrin, a novel immunomodulatory protein in a phase IB trial of patients with refractory solid tumors. *Methods*: Thirty-six patients with metastatic cancer who had progressed on, or were ineligible for, standard chemotherapy received single-agent oral talactoferrin. Following dose-escalation, with no DLTs , patients were randomized to 4.5 or 9 g/day talactoferrin. *Results*: Talactoferrin was well tolerated with apparent anti-cancer activity, particularly in NSCLC and RCC. One patient had a PR (RECIST) and 17 patients (47%) had stable disease (50% disease control rate). Median PFS in the twelve NSCLC and seven RCC patients was 4.2 and 7.3 months, respectively. There was no apparent difference in anti-tumor activity or adverse events between talactoferrin doses. *Conclusions*: Oral talactoferrin was well tolerated. Although evaluated in a small number of patients, talactoferrin appeared to have anti-cancer activity, particularly in NSCLC and RCC and should be evaluated further.

Keywords Talactoferrin · Biologic · Novel therapeutic · NSCLC · Renal cell cancer

Abbreviations

AE	Adverse event
DCR	Disease control rate
CTC	Common toxicity criteria
DLT	Dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HCC	Hepatocellular carcinoma
hLF	Human lactoferrin
IRB	Institutional Review Board
ITT	Intent to treat
LF	Lactoferrin
MTD	Maximum tolerated dose
NK	Natural killer
RCC	Renal cell cancer
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
OS	Overall survival
NSCLC	Non-small cell lung cancer
PFS	Progression-free survival
PMNs	Polymorphonuclear cells
PR	Partial response
RCC	Renal cell carcinoma
TGR	Tumor growth rate
TLF	Talactoferrin: recombinant human lactoferrin
SAE	Serious adverse event
VA	Veterans affairs

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Introduction

Talactoferrin alfa (talactoferrin, TLF), a novel dendritic cell recruiter and activator (DCRA), is a unique recombinant form of human lactoferrin, an important immunomodulatory protein first identified in breast milk. [1] Lactoferrin, found in the highest concentration in milk, is present in normal bodily secretions exposed to the external environment including milk, tears, nasal exudates, saliva, bronchial mucus, gastrointestinal fluids, cervico-vaginal mucus and seminal fluid, and is a major constituent of the secondary specific granules of circulating polymorphonuclear cells (PMNs). Lactoferrin plays an important role in helping to establish the immune system, including the Gut Associated Lymphoid Tissue (GALT), in infants. Talactoferrin is produced in Aspergillus niger, a filamentous fungus, and is structurally identical to native human lactoferrin in all material respects, differing only in its glycosylation. [2] Orally administered talactoferrin mediates a systemic anti-cancer immunological response [3–6] by inducing the recruitment of immature dendritic cells (DCs) from the circulation into the GALT and promoting their maturation. [7, 8] Talactoferrin-mediated DC and effector cell activation in the GALT, which is the largest lymphoid organ in the body, minimizes the effect of tumor-produced anti-immune factors that interfere with the immune system's normal function in clearing tumor cells.

In animal models, talactoferrin inhibited the growth and metastasis of several types of cancer and potentiated the activity of concurrent chemotherapy [4–6, 9, 10]. Oral talactoferrin appeared to be well tolerated in healthy human volunteers. [11] Based on this experience, we conducted a phase IB trial to evaluate the safety and activity of oral talactoferrin in patients with metastatic cancer.

Patients and methods

This was a phase IB study to evaluate the safety and activity of oral talactoferrin in patients for whom no effective therapies were available. Patients were eligible to participate if they had advanced or metastatic cancer with at least one radiologically measurable lesion, and had either failed standard chemotherapy or had no effective therapy available. Subjects were required to have radiologic evidence of progression of their cancer prior to entry into the study. All patients were adults over 18 years of age, with ECOG performance status 0–2 and a minimum estimated life expectancy of 3 months. Any prior chemotherapy, radiation therapy, or surgery must have been completed at least 4 weeks prior to starting the study. Patients were excluded from participation if they had serious uncontrolled infections, were on immunosuppressive drugs, or had other serious health conditions that would impede participation in the study.

The trial was a two-part study involving 36 patients. The primary endpoint was to determine talactoferrin safety and tolerability. The secondary objective was to evaluate talactoferrin's anti-cancer activity. The initial ten-patient dose-escalation phase was designed to evaluate talactoferrin safety and pharmacokinetics and establish a maximal tolerated dose (MTD) (if any), and has been reported previously. [10] The dose escalation phase of the trial used doses of 1.5, 4.5, or 9 g/day. All doses were well tolerated; no dose limiting toxicities were reported, and an MTD could not be defined. As pre-specified in the protocol, in the second part of the study patients were randomly assigned to receive one of the two highest doses (4.5 or 9 g/day) administered in two divided doses. We now present results from the entire 36-patient trial.

Safety endpoints were defined as the occurrence of adverse events as reported by the patients or observed on physical examination or clinical laboratory assessments. Toxicities were graded according to version 2 of the National Cancer Institute Common Toxicity Criteria (CTC). Due to the expected heterogeneity of tumor types, tumor growth rate (TGR) was prospectively defined as an endpoint to evaluate talactoferrin's anti-cancer activity. Additional efficacy endpoints included tumor response rate (RR) by Response Evaluation Criteria in Solid Tumors (RECIST), progression-free survival (PFS) and overall survival (OS).

Patients were enrolled in the dose-escalation phase from November 2002 through January 2003, and in the second part of the study from January 2003 through February 2005. Prior to entering in the study, all patients had a complete history and physical examination, complete blood cell count, serum chemistries and electrolytes, and a radiological tumor assessment. Complete blood counts, serum electrolytes, and chemistries were determined at each visit. Talactoferrin was administered in cycles of 2 weeks on therapy, 2 weeks off therapy, for two cycles (8 weeks). Subjects whose cancer stabilized or otherwise showed evidence of improvement could continue receiving additional cycles of talactoferrin until evidence of cancer progression, provided they did not have greater than grade 2 toxicity. Participants were requested to maintain a diary documenting talactoferrin administration and any side effects experienced.

Tumors were monitored through radiological studies performed at baseline, in week 7, and every 8 weeks thereafter. Target lesions were selected prior to start of therapy and followed using the RECIST [12]. TGR was calculated as growth per week of the target lesion(s) pre and post talactoferrin. PFS was measured from the date of the baseline CT to the earlier of the date of radiological progression or death. OS was measured from the date of the first talactoferrin dose to the date of death.

Table 1 Adverse events observed in at least 10% of patients

Event	Number (%) of patients (*N*=36)	Grade and relationship
Anorexia	6 (16.7%)	All grade 1, not related
Chest Pain	4 (11.1%)	All grade 1, not related
Diarrhea	4 (11.1%)	1 grade 1, possibly related
		2 grade 2, possibly related
		1 grade 2, not related
Dyspnea	4 (11.1%)	All grade 1, not related
Fatigue	4 (11.1%)	1 grade 1, possibly related
		3 grade 1, not related
Hemoptysis	4 (11.1%)	All grade 1, not related
Nasal Congestion	4 (11.1%)	1 grade 1, possibly related
		3 grade 1, not related
Weakness	6 (16.7%)	1 grade 1, possibly related
		3 grade 1, not related
		1 grade 2, not related
		1 grade 3, not related

The study was approved by the Institutional Review Board of Baylor College of Medicine and by the FDA, and all patients gave written informed consent according to institutional and federal guidelines. The talactoferrin used in this trial was a pharmaceutical-grade drug product provided by Agennix.

Results

Patient demographics and enrollment overview

All subjects were United States Veterans seen at a Veterans Affairs (VA) hospital. Consistent with the demographics of the VA patient population, the patient population was overwhelmingly male (34 males, two females). While the majority of the patients enrolled were white (21/36, 58%), 33% (12/36) were African-American, 1 patient (3%) was Native American, and two patients (6%) were Hispanic. All participants were at least 45 years old at their time of enrollment, with approximately three-fourths (26/36, 72%) over the age of 60; the oldest subject was 72.

The study enrolled its maximum of 36 patients. One patient (patient 26) withdrew after a single dose for reasons unrelated to study drug; 35 subjects completed the initial 8-week course. Eighteen participants received additional cycles of talactoferrin treatment, with two continuing for over 3 years on the study medication.

Among the 36 patients enrolled in the trial, a number of different cancer types were seen. The largest groups were patients with non-small cell lung cancer (NSCLC; 12 patients) and renal cell carcinoma (RCC; seven patients). Other cancer types enrolled included four patients with colorectal cancer, three with head and neck cancer, two with esophageal cancer, and one case each of bladder cancer, dermatofibrosarcoma, hepatocellular carcinoma (HCC), pancreatic cancer, small-cell lung cancer, cancer of the renal pelvis, prostate cancer, and two concurrent primary cancers (HCC and NSCLC). ECOG performance status ranged from 0 to 2.

Talactoferrin safety and adverse events

Consistent with our experience in the dose escalation safety phase of this trial, [10] talactoferrin was well tolerated, with no drug-related serious adverse effects (SAE) or grade 3/4 adverse effects (AE), either clinically or in laboratory findings. There were no detectable hematological, renal, or hepatic toxicities, and no apparent dose-dependence to any of the toxicities. A few grade 1 and grade 2 AEs were

Table 2 Details on survival of individual NSCLC patients

Pt. no.	Initials	TLF g/day	Prior treatment regimens	PFS Months	Survival months
7	JSL	4.5	Paclitaxel/carboplatin, radiotherapy	3.9	18.7
8	TCL	9.0	Paclitaxel/carboplatin, radiotherapy	8.1	12.9
9	WJM	9.0	ChemoXRT with cisplatin, paclitaxel/carboplatin	1.8	12.0
11	NEB	9.0	Paclitaxel/carboplatin, radiotherapy, vinorelbine, dietary methionine	2.0	6.1
13	CLE	4.5	VP16/carboplatin, XRT, paclitaxel/carboplatin	2.0	7.5
15	BWD	4.5	Paclitaxel/carboplatin, radiotherapy	4.8	12.7
22	DLD	9.0	None (Patient refused chemotherapy)	6.5	6.8
24	WMA	9.0	ChemoXRT with carboplatin, paclitaxel/carboplatin	7.5	8.0
28	TAB	9.0	Paclitaxel/carboplatin, radiotherapy, docetaxel	5.8	9.6
31	YDR	9.0	ChemoXRT (unknown type)	25+	31
32	DA	4.5	Paclitaxel/carboplatin, docetaxel	1.9	1.9
33	LTE	9.0	Docetaxel/carboplatin	3.0	3.0

observed that could possibly have been related to study drug. Most of the toxicities reported by the patients were constitutional symptoms that are commonly found in patients with advanced cancer. No patient terminated the study or was dose-reduced due to medication toxicity. A listing of all AEs observed in at least 10% of the patients is provided in Table 1.

Antitumor activity of oral talactoferrin

Talactoferrin appeared to have anti-cancer activity in this patient population. The majority of the patients appeared to have a clinical and/or a radiological (defined as disease stabilization or regression) benefit from talactoferrin. At the 2-month CT scan, the tumor size remained stable by RECIST criteria in 18 patients (50% of the ITT patient population). This included one patient who developed a sustained partial response (PR) and four patients with minor responses (shrinkage short of the 30% required for a PR by RECIST).

Since patients with NSCLC and RCC were enrolled in significant numbers, they were analyzed for overall survival and progression-free survival, as prospectively defined in the protocol. Tumor growth rates before and after start of treatment with talactoferrin, another prospectively defined efficacy endpoint, were evaluated for all patients and for patients with NSCLC and RCC.

Activity in non-small cell lung cancer

Twelve patients with metastatic NSCLC were enrolled. Eleven had received prior treatment(s) including chemo-

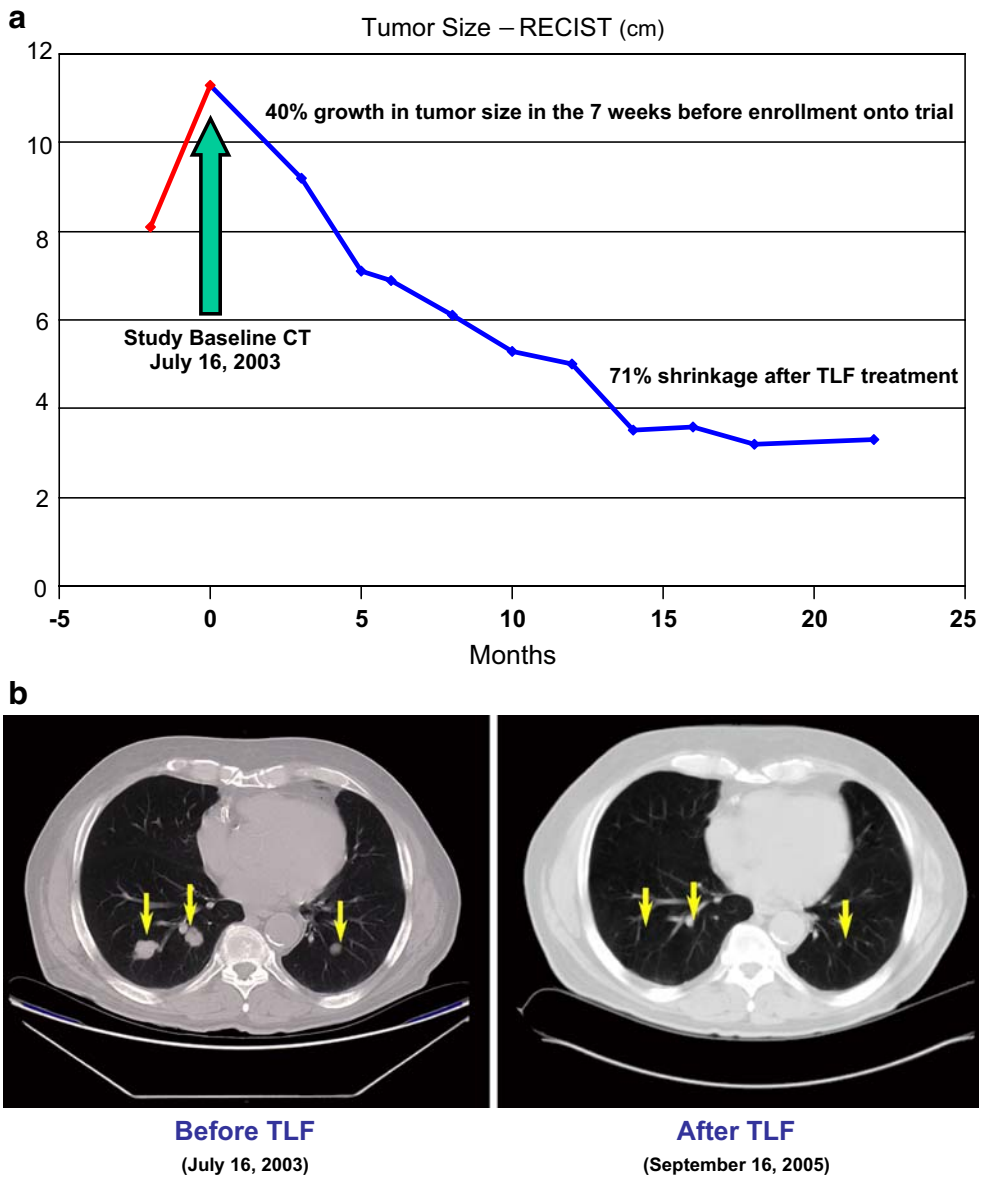

Fig. 1 Time course and CT of tumor response following talactoferrin administration. Patient with metastatic RCC who had failed previous therapy (lesions grew 40%) received oral talactoferrin starting August 7, 2003 (*open arrow*). **a** Shows the change in the sum of the longest diameters of the target lesions over time. **b** Shows CT images at baseline and 22 months after starting oral talactoferrin treatment. *Arrows* indicate target lesions

Table 3 Details on individual RCC patients

Pt. No.	12	19	20	21	29	34	37
Initials	SJM	DWC	LMJ	WJH	SES	BLR	DRW
Age	72	61	73	66	60	67	62
TLF Dose (gm/day)	4.5	9	9	4.5	4.5	4.5	9.0
Histology	Clear Cell	Clear, Spindle Cell	Clear Cell	N/A	Clear, Granular Cell	Clear Cell	Clear Cell
Previous Therapy	Nephrectomy α-interferon, Gemcitabine, Xeloda, SU5416	Nephrectomy, α-interferon, IL2, Methionine restriction	Nephrectomy α-interferon Capecitabine, Gemcitabine, Thalidomide	None	Nephrectomy α-interferon	Radical nephrectomy	Nephrec-tomy
PFS (Months)	3.4	33	34	7.3	4.0	8	4.3
Survival (Months)	3.4	64+	37.5	7.3	6.3	48+	9

radiotherapy and combination chemotherapy regimens (Table 2). One patient (patient 26) withdrew for personal reasons after receiving a single dose of talactoferrin, and two others (patients 32 and 33) received fewer than 28 doses of talactoferrin. Of the 12 enrolled NSCLC patients, seven (58%) had stable disease, including two with a minor response short of a partial response (patients 22 and 28, with 13% and 20% shrinkage by RECIST, respectively, at 4 months). The median progression free survival was 4.3 months, and the median overall survival was 8.8 months. The 6-month survival rate was 83% and five patients (42%) lived for more than a year. Individual patient PFS and survival data is provided in Table 2.

Activity in renal cell cancer

Seven patients with metastatic RCC were enrolled, all of whom received at least 28 doses of study medication. All seven patients achieved at least stable disease, and one patient (no. 20) maintained a partial response for 2 years. The median PFS for the RCC patients was 7.3 months. Two patients (nos. 19, 20) remained progression-free and on drug for 2 years after enrollment on the study. Both these patients also lived over 3 years (one is alive at 64 months) with a third patient still alive 4 years after start of therapy with talactoferrin.

We observed one sustained partial response with talactoferrin. This subject (no. 20) had progressed on a multi-drug regimen of interferon, capecitabine, gemcitabine and thalidomide and his target lesions were growing rapidly prior to receiving single-agent therapy with oral talactoferrin. A 19% shrinkage of his target lesions was noted on his 2-month CT and a PR (>30% shrinkage) was reached at 4 months. The tumor lesions continued to shrink with additional cycles of oral talactoferrin, a late response that is consistent with talactoferrin's immunomodulatory mechanism of action. The tumor burden reached a nadir after 20 months of receiving talactoferrin, having decreased in size by 72% from the baseline sum of longest diameters (Fig. 1). He discontinued talactoferrin 34 months into the study, when he developed a new lung metastasis requiring radiotherapy and died a few months later. Individual patient details are provided in Table 3.

Tumor growth rate (TGR) reduction

Since we enrolled patients with a broad range of tumor types, some of which (e.g. RCC) can be quite heterogeneous, we pre-specified a non-standard secondary efficacy endpoint—assessment of tumor growth rate (TGR). We measured the subjects' TGR before and after starting talactoferrin, a metric that may be relevant to non-cytotoxic or immunomodulatory drug such as talactoferrin. Because the entry criteria specified that all participants were to have had radiologically confirmed progressive cancer in

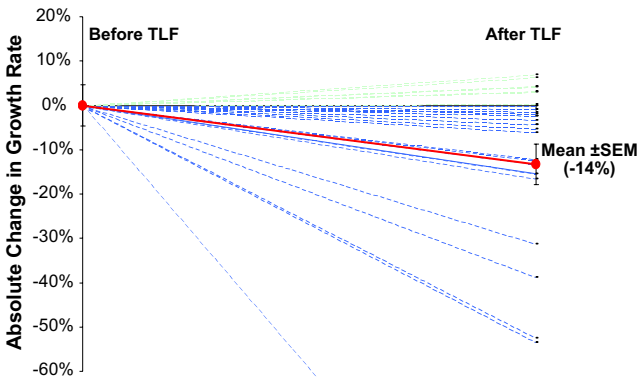

Fig. 2 Tumor growth rate (TGR) before and after talactoferrin administration. *Each dotted line* represents the absolute change in TGR (growth in percent per month) in an individual patient, with the *bold red line* representing the mean (+ SEM). On average, the TGR decreased from 20% a month before talactoferrin to 6% a month after talactoferrin (14% absolute or 70% relative reduction; $P<0.01$ with a two-tailed paired *t*-test)

order to qualify for the study, patients had at least two sets of RECIST measurements available: pre-study and baseline (after enrolling but prior to talactoferrin dosing). These two sets of CT scans allowed TGR to be calculated prior to the patients receiving talactoferrin. For patients with a 2-month CT scan, the TGR following the start of talactoferrin therapy could also be measured.

A total of 29 patients (81%) had a pre-study, baseline, and 2-month CT available, and were evaluable for TGR analysis. Of these, 22 subjects (76%) had a reduction in the TGR (Fig. 2). On average, the TGR decreased from 20% a month before talactoferrin to 6% a month after talactoferrin, a 14% absolute and 70% relative decrease ($P<0.01$). Although involving fewer patients, a relative reduction in TGR was also observed in patients with NSCLC (87%; $P<0.05$) and RCC (98%; $P<0.05$). There was no apparent difference in TGR between patients receiving 4.5 and 9 g/day of talactoferrin (P=0.852).

Discussion

Oral talactoferrin is a novel immunomodulatory molecule that has shown promising antitumor activity in pre-clinical models and appears to be well tolerated in healthy volunteers. [4–9]

We evaluated the safety and activity of oral talactoferrin in late-stage cancer patients. Patients with a variety of tumor types who had failed or were ineligible for standard chemotherapies received single-agent therapy with oral talactoferrin. Talactoferrin appeared to be well tolerated, with no DLTs, MTD or drug-related SAEs.

We evaluated talactoferrin's activity in the entire patient population using a novel endpoint—tumor growth rate (TGR). As shown in Fig. 2, following treatment with oral talactoferrin, the growth rate of prospectively defined target lesions decreased substantially (14% absolute and 70% relative reduction; $P<0.01$). These findings are consistent with results from an independent phase I/II trial [unpublished data], in which cancer patients with solid tumors received 2 weeks of oral talactoferrin following progression on prior therapy. Patients on that study, which included 22 patients evaluable for TGR, also had a 70% relative decrease in TGR (16.9% to 5.1% growth per month; $P<0.01$). Tumor growth rate may be helpful in the early evaluation of non-cytotoxic agents, particularly in phase I/II studies with a mixture of cancer types, or in a disease like RCC that has high tumor heterogeneity. [13] In small early-stage trials where a control arm is not available, TGR may provide an additional metric to help evaluate anti-cancer activity of novel agents, since the patient acts as his or her own control. Since this metric requires a pre-study CT in order to establish the pre-treatment rate of tumor growth, the approach would be most applicable in patients who have demonstrated progression on previous therapy. Our experience suggests that the utility of TGR should be evaluated further.

The study included a heterogeneous patient population with a variety of cancer types. We were able to evaluate PFS and OS in the cancer types where we had the highest number of patients enrolled—those with NSCLC and RCC (12 and seven patients, respectively). Indications of anti-cancer activity were observed in both cancer types. Based on these results, follow-up phase II studies have been conducted with indications of anti-cancer activity in patients with both NSCLC [14–16] and RCC [17]. Talactoferrin is now in phase III clinical development for the treatment of cancer. The study reported here provided the first evidence of talactoferrin's anti-cancer activity in humans.

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