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## Original Paper

# A Pilot Study of the Safety and Effects of the Matrix Metalloproteinase Inhibitor Marimastat in Gastric Cancer*

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**The aim of this study was to evaluate the safety and tolerability of 4 weeks administration of marimastat, and to seek evidence of biological activity as observed by changes in the endoscopic appearance of the gastric tumours. 35 patients with advanced, inoperable gastric or gastro-oesophageal tumours were recruited. The dose of marimastat was reduced from the starting dose of 50 mg twice daily (6 patients) to 25 mg once daily (29 patients). 31 completed the 28 day study period. Marimastat was generally well tolerated, with the principal treatment-related toxicity being pain and stiffness of the musculoskeletal system. These symptoms occurred more frequently at the higher-dose, and increased to involve a total of 13 patients (37%) with longer-term treatment. The events were usually rapidly reversible on drug discontinuation. 3 patients receiving prolonged treatment experienced more severe symptoms, with the development of skin thickening and contractures in the hands. At endoscopy, 10 patients showed an increased fibrotic cover of the tumour, 8 had decreased haemorrhagic appearance, and in at least 2 cases where comparative tumour histology was assessable, there was evidence of increased stromal fibrotic tissue.** © **1999 Elsevier Science Ltd. All rights reserved.**

**Key words: marimastat, metalloproteinase inhibitors, gastric cancer, histopathological effects**
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## INTRODUCTION

ALTHOUGH THE incidence of gastric cancer has declined steadily over the past 50 years [1] it remains the second commonest cause of cancer-related mortality worldwide [2]. The majority of gastric cancers in Western countries are advanced at presentation [3] and, therefore, not amenable to curative resection. Systemic cytotoxic treatments for advanced gastric cancer have achieved encouraging response rates, although there is little to choose between regimes [4–7], and any evidence of survival benefit remains contentious. It is apparent, therefore, that results with conventional treatments are less than satisfactory, and alternative therapeutic modalities are required. One such possibility is the pharmacological inhibition of matrix metalloproteinases (MMPs), a group of enzymes which have been implicated in the pathogenesis and progression of gastric cancer.

In the healthy individual, MMPs are responsible for the degradation of extracellular matrix that occurs during tissue formation and remodelling [8]. However, unregulated and excessive MMP activity is the pathological process responsible for many of the behavioural characteristics of diseases such as cancer [9], inflammatory bowel disease [10], rheumatoid arthritis [11] and other diseases [12–14]. In gastric cancer specifically, tumour tissue has shown overexpression of MMPs when compared with normal mucosa; expression of MMP-2 (gelatinase A) and MMP-7 (matrilysin) increases with histological grade and depth of invasion [15, 16]; and high MMP-2 and MMP-9 (gelatinase B) levels have been shown to be of prognostic significance for poor overall

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survival [17]. Plasma concentrations of MMP-9 measured during a one-step sandwich enzyme immunoassay were found to be higher in patients with gastric cancer than in normal subjects and this level correlated with the stage of the disease [18]. Inhibition of MMPs may, therefore, represent a successful strategy for the treatment of this disease.

Marimastat is a potent and reversible inhibitor of MMPs, exhibiting $IC_{50}$s in the nanomolar range against MMP-1 (interstitial collagenase), MMP-2, MMP-3 (stromelysin-1), MMP-7, MMP-9 and MMP-12 (metalloelastase). It has little or no activity against unrelated metalloproteinases such as enkephalinase. Using animal cancer models, both marimastat and its predecessor, batimastat, have been observed to inhibit tumour growth and metastasis [19]. Administration of marimastat to healthy volunteers suggested a rapidly absorbed and well-tolerated drug, with pharmacokinetic data indicating that total daily doses of 50–100 mg would achieve trough blood levels greater than 40 μg/l (six times the $IC_{50}$s for the major MMPs) [20].

Further development of marimastat was problematic in that, as a tumoristatic drug, it was not expected to cause the reduction in tumour size associated with conventional cytotoxic drugs. Rather, it was thought that treatment with marimastat might result in an increase in peritumoral fibrotic tissue, as seen in some preclinical studies [21], with minimal effects on the size of the underlying tumour. The use of radiological or clinical measurements of tumour response or progression would, therefore, probably fail to detect clinically relevant activity, and a novel approach to such trials in patients with cancer was required.

Two strategies were chosen to assess the drug across a range of tumour types. The first strategy used changes in the rate of rise of serum tumour markers to indicate biological activity [22, 23]. These studies were conducted in patients with colorectal, ovarian, pancreatic and prostate cancers, where tumour markers are commonly expressed and have utility in disease management. The second strategy was to look for macroscopic and microscopic changes in tumour appearance consistent with a drug effect. This paper reports the results of the first completed study using the second approach, in which the effects of marimastat on endoscopic and histological appearances of gastric and gastro-oesophageal carcinomas are assessed, and the adverse event profile of the drug is described.

## PATIENTS AND METHODS

*Patients*

Patients were selected for this study who had inoperable and histologically proven primary or recurrent gastric or gastro-oesophageal carcinoma. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and a predicted survival of 3 months or more was required, although no stipulation was made as to whether the tumour needed to be clearly progressive or not. Entry into the trial was to be delayed for 2 weeks after open surgery, and for 1 month if chemotherapy, radiotherapy or hormonal treatment had been received. Patients were excluded if bilirubin was greater than twice, liver enzymes were greater than three times, and creatinine greater than twice the upper limit of normal, or if albumin was less than 2.5 g/dl.

Patients were enrolled by two centres, Queen's Medical Centre, Nottingham and the Glasgow Royal Infirmary, Glasgow. The protocol and protocol amendments were reviewed by the research ethics committee at each investigational centre and approved. All patients provided witnessed written informed consent to participate in the study, and the study was conducted in accordance with the European Guidelines on Good Clinical Practice.

*Objectives*

This study aimed to assess the safety and tolerability of 4 weeks administration of marimastat, and to evaluate the drug for evidence of biological activity as measured by changes in the endoscopic and histological appearance of the tumours.

*Treatment*

Capsules containing 5, 10, 25 or 50 mg of marimastat were provided by British Biotech Pharmaceuticals Ltd, Oxford, U.K. It was originally intended that patients would receive doses of 50 mg twice daily for a period of 28 days. The first protocol amendment allowed the continued administration of marimastat beyond 28 days in patients who were thought by the investigator to have shown a good response and who had no clinical evidence of tumour progression. Dose reduction was possible where patients experienced marimastat-related toxicity of less than grade 3. Toxicity at or above this level dictated exclusion from marimastat continuation.

Selection of a starting dose with a potentially cytostatic drug is problematic in that there are no validated surrogates on which to base activity in terms of tumoristasis. In the event, the starting dose was selected on the basis of data from healthy volunteer studies [20], which suggested that total daily doses of 50–100 mg would achieve trough blood levels of marimastat of greater than 40 μg/l, sufficient to exceed six times the $IC_{50}$s for MMP-1, MMP-2, MMP-7 and MMP-9. However, preliminary pharmacokinetic data from this and other studies in patients with advanced cancer [22, 23] indicated that trough blood levels were several times higher than those predicted from healthy volunteer studies. This was thought to be explained by a combination of factors including increased age, reduced hepatic and renal function, and a considerably increased level of plasma protein binding of the drug in patients with advanced cancers (British Biotech., Oxford, U.K.). Also, musculoskeletal side-effects were observed in a substantial number of patients receiving doses of this order. A conventional study assessing a maximum tolerated dose had observed that 5 out of 6 patients treated at 100 mg twice daily developed an 'inflammatory polyarthritis' and recommended that lower-doses be explored for further trials [24]. Therefore, after the first 6 patients were enrolled, it was decided to continue the study using a lower-dose of 25 mg once daily. The change was the subject of a second protocol amendment.

Endoscopic examination of the tumours was performed using Olympus Evisystem flexible gastroscopes, and photographs were taken on day 0 before the first dose, and on day 28. Any changes in macroscopic and microscopic tumour appearance between days 0 and 28 were noted. Specifically, changes in haemorrhagic appearance and size were described, as was the presence or absence of a white fibrous coating previously noted in animal studies [21]. Assessments of the tumours were performed both by the endoscopist at the time of the examination and by subsequent independent assessment of the photographs resulting from this examination. Multiple biopsies were taken of the tumours at each endoscopy session to minimise any sampling error. Biopsies taken at endoscopy were fixed in formalin and underwent routine

processing in the Department of Histopathology, Queen's Medical Centre, Nottingham, U.K. 5 μm Sections (5 μm) were stained with haematoxylin and eosin and assessed by a single unblinded consultant histopathologist. Variables recorded included degree of differentiation of the tumour, presence of chronic and acute inflammation, amount of stroma and evidence of necrosis.

All adverse events were recorded, whether they were considered related to marimastat or not, and allocated a National Cancer Institutes (NCI) Common Toxicity Criteria (CTC) Grade. Blood samples were taken at screening, day 0 (predose), day 7 and day 28 for evaluation of haematology, biochemistry and pharmacokinetics. Monitoring continued for those patients receiving marimastat beyond day 28. Urinalysis, vital signs and electrocardiograms were monitored throughout the study.

*Statistical analysis*

No formal statistical assessment of the results from this pilot study was planned. It was anticipated that safety and efficacy end-points would be summarised and tabulated as appropriate.

## RESULTS

*Patient population*

35 patients entered the study, of whom 4 did not complete the 28-day treatment period. One patient died, 1 withdrew to receive other therapy, 1 did not wish to continue, and 1 discontinued due to an adverse event. Of 31 patients completing 28 days of treatment, 14 continued receiving marimastat.

Patient characteristics are listed in Table 1. All patients had histologically confirmed gastric adenocarcinoma which was deemed inoperable, the large majority being stage IV (American Joint Committee on Cancer, 1988). Most patients had undergone a previous palliative surgical procedure, although none had received chemotherapy or radiotherapy.

*Safety assessments*

35 patients were assessable for safety and tolerability. Adverse events occurring in at least 2 patients during the 28 day study period are presented in Table 2, which incorporates all reported events, whether thought to be related to marimastat or not. 14 out of 29 patients (48%) receiving 25 mg once daily and 5 out of 6 (83%) receiving 50 mg twice daily experienced adverse events. Events related to the musculoskeletal and gastrointestinal systems were most commonly reported. All the musculoskeletal adverse events were thought to be possibly related to marimastat, while most gastrointestinal events were thought to be related to the underlying disease.

There were seven events occurring with a NCI CTC grading of 3 or more, 4 at 50 mg twice daily and 3 at 25 mg once daily. Five of these were related to the gastrointestinal system (nausea, vomiting and diarrhoea). One of these cases (grade IV diarrhoea) was thought to be possibly related to marimastat. The other 2 cases (grade 3 musculoskeletal symptoms and grade 3 flu-like symptoms) were also thought to be probably or possibly related to marimastat. Overall, there was no pattern of NCI CTC toxicity suggesting a drug-related toxicity other than that relating to the musculoskeletal system. During the study, 9 patients suffered adverse events requiring dose reduction or temporary discontinuation, 2 at 50 mg twice daily and 7 at 25 mg once daily. These comprised six events relating to the musculoskeletal system, and 3 cases of vomiting (1 patient also developing jaundice).

The principal side-effect of marimastat reported in this study was related to the musculoskeletal system, with most events being reversible. Symptoms reported in the first 28 days of treatment were arthralgia (5 patients) and myalgia (2 patients) most commonly in the upper limbs, joint stiffness, neck pain and neck stiffness (each reported in 1 patient). In total, 13 patients (37%) developed musculoskeletal events, the frequency of which increased during the continuation period of therapy. Arthralgia (9 patients) and joint stiffness (3 patients) became more common, and there was a single report of adductor longus tendinitis. 5 patients treated with 25 mg once daily marimastat required dose modification or treatment withdrawal as a result of musculoskeletal events, occurring at a mean of 45 days. Amongst those patients continuing to use the drug beyond 3 months there were 4 cases of subcutaneous skin thickening of the palmar surface of the hands, associated with contracture of the digits in three cases. These changes were described at the time as resembling Dupuytren's disease, but were to a large extent reversible. Of those patients whose symptoms required dose modification or drug withdrawal, the majority were able to resume treatment at the same or a lower dose.

Five serious events were reported as being possibly related to marimastat, including cases of disseminated carcinoma, chest pain, hepatic dysfunction, asthenia and pulmonary embolism. In each case these events were considered to be more probably related to the primary disease. There were no

*Table* 1. *Patient characteristics*

| Characteristic | |
|---|---|
| No. of patients | 35 |
| No. patients completing 28 days treatment | 31 |
| No. patients continuing treatment after day 28 | 14 |
| Age median (range) | 73 (38–88) years |
| Tumour stage | |
| Stage II | 4* |
| Stage III | 3 |
| Stage IV | 23 |
| Unknown | 5 |
| No. of patients with prior palliative surgery | 22 |
| No. of patients with visceral metastases | 14 |

*Patients unfit for surgery due to concomitant medical conditions.

*Table* 2. *Summary of adverse events occurring in* 28*-day study period (all causalities)*

| | 25 mg once daily (%) | 50 mg twice daily (%) | Total (%) |
|---|---|---|---|
| Number of patients with adverse events | 14/29 (48) | 5/6 (83) | 19/35 (54) |
| Arthralgia | 4 (14) | 1 (17) | 5 (14) |
| Myalgia | 1 (3) | 1 (17) | 2 (6) |
| Dysphagia | 1 (3) | 1 (17) | 2 (6) |
| Nausea | 1 (3) | 1 (17) | 2 (6) |
| Diarrhoea and Vomiting | 4 (10) | 2 (33) | 6 (14) |
| Disseminated carcinoma | 2 (7) | 0 | 2 (6) |

obvious adverse trends in laboratory values with marimastat treatment, although many out of range values were recorded both before and during treatment. Specifically, there was no suggestion of myelotoxicity associated with marimastat's use.

*Efficacy assessments*

*Pharmacokinetics.* Plasma levels of marimastat were obtained on day 0, 2 h after initial dosing and at day 28. The mean 28-day trough plasma level of marimastat for those patients receiving 50 mg twice daily was 264 μg/l, several-fold higher than that predicted from the healthy volunteer studies [20], and consistent with the excess musculoskeletal toxicity seen at that dose. The mean 28-day trough levels for those patients subsequently recruited to receive 25 mg once daily was 43 μg/l. These results were similar to mean trough plasma levels obtained from patients with other advanced cancers [22].

*Macroscopic tumour assessment.* Changes in the macroscopic appearance of the tumour were recorded in two ways. Firstly, changes were noted by the investigator at the day 28 endoscopy, and specific record was made of the macroscopic changes with respect to haemorrhage, fibrous cover and tumour size. This assessment is presented in Table 3. Secondly, a later review of the photographs taken at this examination was made. Unfortunately, many of the photographs were not considered assessable at the second review because of variable image quality compared with the predose photograph. However, in 3/6 patients treated with 50 mg twice daily, and 7/29 patients treated with 25 mg once daily, a definite increase in fibrous cover of the tumour was observed when pre- and postdose photographs were compared. Importantly, this change was not limited to the mucosal surface, as the operators described gritty, bloodless tissue upon biopsy of the tumour. Figure 1 shows endoscopic photographs of a patient at screening and after 28 days of treatment. 6 of 10 patients with increased fibrotic cover also showed a decrease in haemorrhagic appearance and this too is apparent in Figure 1.

Tumour size was recorded at endoscopy, in most cases using an instrument with gradations at 2 mm intervals. This was inserted into the endoscope via the biopsy channel and positioned beside the tumour in the subsequent photographs. The majority of photographs deemed assessable (14/24) showed no change in size, although in 3 cases a reduction in tumour size was observed.

*Microscopic assessment.* Because of the nature of endoscopic biopsy specimens, independent comparative assessment at screening and after 28 days of treatment was only possible for 25 patients and few conclusions can be drawn from this data set. There were no changes in either the degree of differentiation of the tumours or the presence of necrosis after 28 days. No trend was identified in the assessment of acute or chronic inflammatory infiltrate. 12 of 25 patients had at least moderate amounts of fibroblastic stroma seen in

*Table 3. Summary of macroscopic changes from baseline at day 28 based on endoscopic photographs*

| | Decrease | Increase | No change/not assessable |
|---|---|---|---|
| Haemorrhage | | | |
| 50 mg bd | 2 | 1 | 3 |
| 25 mg od | 6 | 5 | 18 |
| Fibrous cover | | | |
| 50 mg bd | 0 | 3 | 3 |
| 25 mg od | 0 | 7 | 22 |
| Size | | | |
| 50 mg bd | 1 | 3 | 2 |
| 25 mg od | 2 | 3 | 24 |

bd, twice daily; od, once daily.

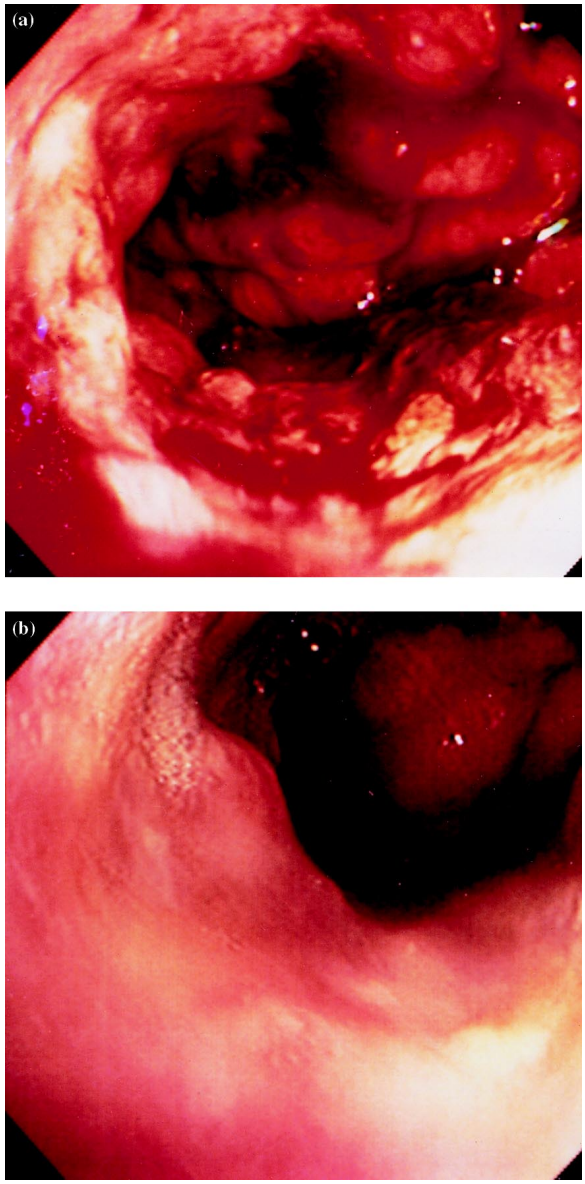


**Figure 1. Endoscopic photographs of a patient 1 at (a) screening; and (b) after 28 days of treatment with marimastat. This 69-year-old man underwent laparotomy for gastric cancer but after trial dissection was found to have inoperable disease with extensive local spread. Initial gastroscopy revealed a large, ulcerating and circumferential tumour in the body of the stomach. He received marimastat for 28 days at 50 mg twice daily, after which endoscopy confirmed a white fibrous appearance with reduced contact bleeding and absence of blood in the lumen. Endoscopic biopsy suggested that the change was not limited to the tumour surface. Histology confirmed increased stroma to tumour ratios compared with the biopsies before treatment. Endoscopic and histological changes were maintained up to the 15 month endoscopy. The patient remained in the study for 17 months although requiring dose reductions and interruptions in therapy because of musculoskeletal adverse events. He died as a result of a chest infection 17 months after entering the trial, at which point his gastric cancer was considered stable. Magnification ×50.**

screening biopsies, so identifying any increase in fibrous tissue during treatment was difficult, although in two of these patients the presence of fibroblastic stroma was more marked at day 28 than at screening. Of the other 13 patients, 2 were reported as showing an increase in the fibrous stroma:tumour ratio in biopsies at the day 28 endoscopy (Figure 2). Both these patients displayed macroscopic changes of an increase in fibrous cover. In one patient the fibrous changes were maintained at all subsequent biopsies up to and including month 15. 2 more patients showed evidence of increased fibrous stroma at some point during treatment other than at day 28 although the day 28, macroscopic examination did not confirm an increase in fibrous cover. A final patient showed altered tumour morphology with loss of signet ring pattern.

## DISCUSSION

This study demonstrated good oral bioavailability of marimastat in patients with advanced gastric cancer. Higher trough plasma levels of marimastat were seen than would have been predicted from studies of the drug in healthy volunteers, and this was consistent with findings from studies of marimastat in patients with other advanced cancers. It is believed that the differences in marimastat pharmacokinetics between young healthy males and older patients with advanced malignancy relates primarily to increased plasma protein binding and reduced liver and renal function in the latter group. It is of note that the group of patients in this study, in whom dysphagia is a common problem, were all able to comply with the study medication and have demonstrated good drug absorption despite an often grossly abnormal upper gastrointestinal tract. At the lower-dose level of 25 mg once daily, the plasma trough levels of marimastat met the target of 40 μg/l or six times the $IC_{50}$s for MMP-1, MMP-2, MMP-7 and MMP-9.

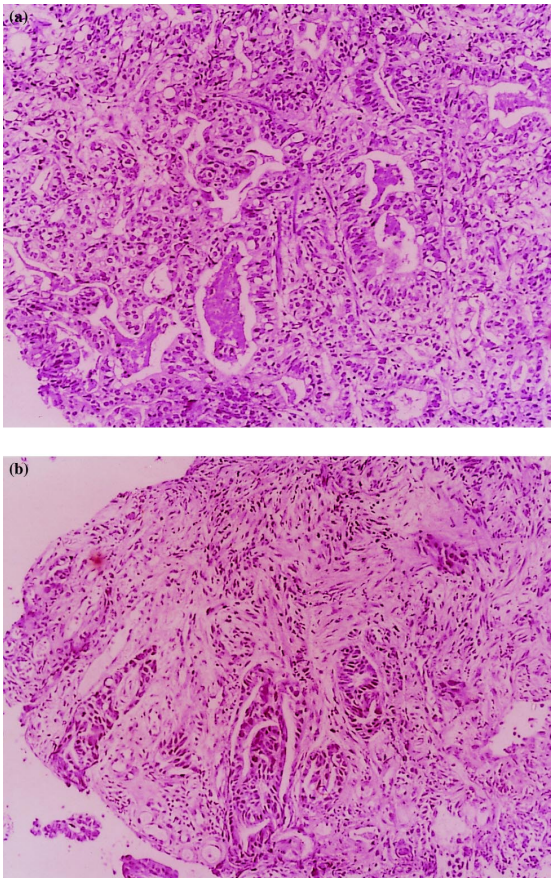


**Figure 2. Histological appearance of biopsy specimens at (a) screening; and (b) at day 28 in patient 1, indicating a marked increase in fibrous stroma with treatment. Magnification ×50.**

Marimastat was reasonably well tolerated, with musculoskeletal events emerging as the principal treatment-related side-effects. The occurrence of these events was seen to be related to both dose and duration of therapy, indicating that a dose of 25 mg once daily was a more suitable choice for longer-term treatment than the initial dose of 50 mg twice daily. More than one-third of patients developed musculoskeletal side-effects within the study period, which were for the most part reversible.

Although arthralgia and myalgia were most commonly reported, two typical conditions were characterised; firstly, an event clinically indistinguishable from frozen shoulder with painful limitation of abduction and some loss of function, and secondly, a condition resembling Dupuytren's contracture, with thickening of the palmar fascia and flexion contractures of the digits. Worsening of a pre-existing Dupuytren's contracture was also observed. These events were consistently worse in the dominant side. Such effects are of great interest not only because they imply that this drug is biologically active in these subjects, but also because it may illuminate the shared aetiology of these two common clinical problems [25]. It is postulated that inhibition of normal peri-articular collagenase activity in the process of normal joint remodelling results either in lack of repair or inappropriate collagen deposition, which may in turn result in inflammation and restricted movement. There was no other observed pattern of adverse events or laboratory abnormalities which would not be typical of a population with advanced gastric cancer.

It may be suggested that the changes in the macroscopic appearance of the tumours were artefactual, perhaps because of use of concomitant medications with activity at the gastric mucosa, or superficial only, without substantial impact on the characteristics of the tumour as a whole. It is reassuring, therefore, to note that there was no association of the observed changes with use of ulcer healing drugs. Indeed, of the 10 patients developing the fibrous coating on the surface of the tumours, only 4 were found to have taken such agents (ranitidine or omeprazole) during the study period.

A limited number of comparative histology specimens also revealed changes consistent with the macroscopic findings. The apparent increase in fibrotic tissue in the gastric tumours of some patients is one of the most striking indications of the biological activity of marimastat, and was observed at a dose range of marimastat in which effects on tumour markers had previously been noted [22]. Such fibrotic changes are consistent with the postulated mechanism of action of marimastat, and have been seen in some animal cancer models treated with metalloproteinase inhibitors [21]. However, this finding is not always present in the animal models, even in the presence of reduced tumour growth [26], indicating that any assessment of the presence or absence of antitumour drug activity requires more than a simple measure of stromal fibrous tissue.

In conclusion, allowing for the fact that the study was not blinded and the variables measured were subjective, there were still encouraging signs of a biological effect of the drug on the macroscopic appearance of the tumours. These findings

indicate that a longer-term, controlled study of marimastat in patients with gastric cancer is warranted, although close monitoring of the long-term tolerability of this agent will be mandatory.


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