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Marimastat (BB2516): Current status of development

Abstract Marimastat (BB-2516) is the first matrix metalloproteinase inhibitor to have entered clinical trials in the field of oncology. It has excellent bioavailability and has completed phase I and II trials. Phase I studies involved healthy volunteers who received short courses of marimastat; these were well tolerated. Symptoms experienced by many patients with various malignancies included severe joint and muscle pain which were debilitating in >60% of patients at doses >50 mg bid. These symptoms were reversible on discontinuation of the drug, and their incidence has been decreased by using marimastat 10 mg bid, the dose used in current studies. Phase II studies involved the use of serum tumor markers as surrogate indicators of antitumor activity. Six studies in colorectal, ovarian, and prostate cancer have been completed and pooled analysis has demonstrated a dose-dependent biological effect (as defined by the authors); 58% of patients respond at doses >50 mg bid. Effects on tumor markers were associated with increased survival. Small phase II studies have suggested potential activity in pancreatic and gastric cancer and have demonstrated the safety of combining cytotoxic chemotherapeutic agents with marimastat. Ongoing phase III studies are investigating the effects of marimastat in addition to chemotherapy in the treatment of small cell lung cancer and pancreatic and gastric carcinoma.

Key words Marimastat · Clinical development · BB2516

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Introduction

Matrix metalloproteinases (MMPs) are a family of related proteinases which appear to be important for the breakdown of extracellular matrix proteins [7]. At least 16 MMPs have been identified, all of which are controlled by a group of inhibitors known as tissue inhibitors of metalloproteinases (TIMPs) [11].

Increasing evidence indicates that regulation of MMP activity is abnormal in many types of malignancy [4]. Increased activity of these enzymes may facilitate metastasis by allowing tumor cells to gain access to a vascular or lymphatic pathway. These enzymes also allow local tumor growth by providing a physical space for new cells to expand into. MMP inhibitors (MMPIs) have been developed with the aim of blocking the activity of MMPs in the hope that both local tumor growth and metastasis can be inhibited [5]. The results of preclinical experiments have strongly supported their potential role in treating neoplasia, and the clinical development of several metalloproteinase inhibitors is therefore underway. This review focuses on the current status of the use of marimastat (BB-2516) which was the first MMPI to enter clinical trials and for which the most information is currently available in the field of oncology.

MMP activity in cancer

Local tumor growth involves the breakdown of extracellular matrix proteins and the MMPs appear to be intimately involved with this process [7]. The 16 members of the MMP family identified to date are all secreted in an inactive form, with activation occurring extracellularly. It is the activated form that is controlled by the group of inhibitors termed TIMPs [11].

In malignancy, both the regulation and expression of MMP activity are abnormal: MMP expression increases with higher tumor grade and stage [11]. TIMP expres-

sion may also be elevated within tumors. The increase in MMP activity appears to allow tumors to remodel their environment, allowing space for growth and the development of supporting stroma including angiogenesis. Access to vascular or lymphatic channels is also facilitated by increased MMP activity such that metastasis of tumor cells may occur. Given the pivotal role that MMPs appear to have in the local and distant development of neoplasia, over the past 15 years inhibitors of MMP activity have been developed in the hope that they would provide a novel and effective means of treating various malignancies.

Development of MMPIs

Natural inhibitors of MMP activity were originally considered for clinical development. Unfortunately the TIMPs, which showed activity in models of tumor invasion, metastasis, and angiogenesis, are of limited clinical potential as they are proteins which cannot be administered systemically on a long-term basis. The first synthetic MMPIs were developed in the early 1980s. These were pseudopeptide derivatives based on the structure of the collagen molecule at the site of initial cleavage by interstitial collagenase. The inhibitor binds reversibly at the MMP active region utilizing a zinc-binding group. Several zinc-binding groups have been tested, with hydroxamates appearing to be the most useful and being employed in the majority of inhibitors currently in clinical development.

Batimastat was the first compound to enter clinical trials but its development was hampered by poor bioavailability. Chemical modification of this compound resulted in the synthesis of marimastat (BB-2516), which retains the activity of its predecessor but has excellent oral bioavailability.

Preclinical studies

Early in vitro studies focused on the effects of MMPIs and recombinant TIMPs. These inhibitors were found to block tumor cell invasion through matrix barriers in vitro and inhibit organ colonization in experimental metastasis models in vivo [2, 9, 15].

Subsequent investigations focused on the potential of MMPIs to inhibit the growth of established tumors either in their primary or secondary sites [3, 17, 18]. A variety of human tumor xenografts have been grown in nude mice and subsequently exposed to batimastat. The number and size of liver metastases were significantly reduced in the batimastat-treated animals compared with controls and, interestingly, the primary tumors showed marked central necrosis [18]. This may be the result of antiangiogenic activity or of restriction of invasive growth causing increased interstitial pressure and constriction of microvessels. Transfection of tumors with TIMP-2 can cause fibrotic tissue to grow around the tumor mass with subsequent marked reductions in tumor growth and local invasion [8]. Similar effects have been observed with human xenografts treated with batimastat [7]. For some tumor cell lines, exposure to MMPIs appears to slow the rate of growth compared with that of controls rather than cause a reduction in tumor volume [8].

The effects of MMPIs on angiogenesis have also been examined. Batimastat reduces the angiogenic response to heparin in vivo and in Matrigel implants to levels comparable to that in controls. It also inhibits the invasion of HUVEC cells through Matrigel in vitro [4]. Ilomastat is able to inhibit angiogenesis in the chick chorioallantoic membrane assay and a rat cornea model [5].

Recent studies have investigated the potential of combining MMPIs with cytotoxic chemotherapy. Murine Lewis lung carcinoma growth and metastasis are inhibited significantly more effectively by the combination of MMPI and cyclophosphamide than by either of the two compounds alone [16]. Batimastat and cisplatin have been shown to be significantly more effective than either agent alone in prolonging survival in an animal model of human ovarian carcinoma, and toxicity does not appear to be increased [10].

Thus there appears to be good preclinical data to suggest that MMPIs may have a role in the treatment of malignancy both by reducing the rate of growth and, potentially, reducing the size of established primary and secondary disease. They may also reduce the metastatic potential of many types of tumor. Clinical trials with a variety of endpoints have therefore been initiated to examine the potential role of MMPIs in the treatment of human cancer.

Clinical trials with marimastat

Marimastat was the first orally bioavailable MMPI to enter clinical trials. Development has been complex and difficult as it represents an entirely new approach to therapy for which established endpoints for chemotherapy studies are inappropriate. Despite the problems, many interesting results are now becoming available.

Phase I studies

Phase I evaluation of marimastat was performed in 31 healthy volunteers in two placebo-controlled, escalating-dose studies [12]. In the first study, single doses of between 25 and 800 mg were administered. Full pharmacokinetic profiles were obtained and peak plasma concentrations were observed at 1.5–3 h after administration. Peak levels were approximately proportional to dose, as was the area under the curve. The terminal elimination half-life was 8–10 h. No toxicities were seen in this study.

The second study involved administration over 6.5 days with 3 incremental dosages of 50 mg, 100 mg, and 200 mg bid. The pharmacokinetics were similar to those from the single-dose studies and there was no evidence of drug accumulation. Small but reversible elevations in liver transaminases were noted in the repeat dosing study, particularly at doses of 200 mg bid. Other adverse effects were mild and occurred at a similar frequency to those subjects on placebo.

The main side effect associated with marimastat was not detected in this one-week study but became apparent only after repeated administration to cancer patients at 50–100 mg bid for >1 month [13]. Of those receiving the higher doses, >60% developed joint and muscle pain and swelling which could be severely debilitating. The events were reversible but often required a 2–4-week break from treatment. There is increasing evidence that the pharmacokinetics of marimastat differ between patients with cancer and healthy volunteers, with higher plasma concentrations being seen in the former group. This may result from increased plasma protein binding and altered hepatic and renal functions, and could partly explain why these side effects were not observed in any of the early studies.

Phase II studies in patients with cancer

The clinical development of MMPIs in patients with malignancy requires a different strategy than is used with other anticancer drugs. Although some preclinical models suggest that tumor volume reduction may occur through effects on angiogenesis, classical responses would not be expected from an agent that is not cytotoxic. A different approach was therefore adopted. Changes in cancer antigen levels were used as surrogate markers to indicate the potential biological effects of marimastat in the early phase II trials. These involved six parallel phase II studies conducted in North America and Europe [13]. Patients were entered if they had a ≥25% rise in markers prior to entry to the trial. This rise had to be documented over 4 weeks in five of the studies (one study of colorectal cancer in the USA involved a 12-week observation period). Two of the studies measured carcinoembryonic antigen (CEA) in advanced colorectal cancer and two measured CA125 in ovarian cancer. CA19-9 and prostate-specific antigen (PSA) were measured in the remaining trials in pancreatic and prostate cancer, respectively.

After the observation period, patients received marimastat at doses of 25 mg bid escalating in cohorts to 75 mg bid. Treatment was given over 4 weeks with measurement of tumor markers at the beginning and end of this period. Dose reductions were permitted for toxicity. Definitions of response were that a partial biological effect (PBE) was a ≤25% rise in markers over the 4-week treatment period and a biological effect (BE) was a fall in markers during this period.

A total of 415 patients were recruited to the trials, with similar numbers in each of the six studies. Compliance with the protocol was disappointing, with only 54% of patients completing treatment with investigations performed at all the required time points. Marker measurements were either missing or taken at incorrect times in 46% of patients. An intention-to-treat analysis was possible in 75% of patients for whom some data were available.

The trials were originally designed with the expectation that an upper dose of 100 mg bid would be administered. Unfortunately, toxicity became a major problem after one month of therapy in the majority of patients: 68% of those who received doses ≥25 mg bid developed arthralgia, myalgia, and tendinitis, predominantly in the upper limbs. This was clearly dose and time dependent. Resolution of the symptoms usually occurred after a 2–4-week break in treatment. No other serious side effects were observed, but occasional episodes of skin rash and fatigue occurred. Doses were reduced to between 2 and 10 mg bid to reduce the incidence and severity of toxicity after the first 133 patients had been enrolled.

A pooled analysis of activity in all the studies indicated that there appeared to be a dose-dependent increase in the frequency of BE/PBE (Table 1). The median rise of marker levels during marimastat treatment was significantly lower than that during the pretreatment period at dose levels ≥20 mg. There was no apparent difference in the magnitude of the effect in each of the tumor types, although the number of evaluable patients in each of the studies was too small to make a meaningful statistical analysis.

An obvious concern with this approach is that changes in levels of these tumor markers have never been validated as indicating definite anticancer activity and no correlation with objective tumor measurements was made in these studies. Of interest, however, was that survival curves indicated a significantly greater median survival time for those who achieved a BE/PBE than for those in whom marker levels continued to rise (350 vs 200 days, $P = 0.0001$), although such an observation clearly must be interpreted with caution.

Pharmacokinetic data were obtained for several patients and revealed marked intersubject variation at each dose level. There appeared to be an approximately linear relationship between dose and trough, with the mean trough being >6-fold the IC_{50} for MMPs at doses ≥20 mg. The troughs were higher than had been seen in previous studies with healthy subjects and may account for the toxicity seen in cancer patients. The pharmaco-

Table 1 Percentage of patients experiencing BE or PBE during phase II studies of marimastat in advanced malignancies

Dosage	BE/PBE (%)
2–5 mg qd	10/30
5–10 mg qd	15/20
10–25 mg qd/bid	20/25
25 mg bid	25/28
50–75 mg bid	40/18

kinetic results suggest that serum marimastat levels should be adequate for MMP inhibition at the currently recommended dosage of 10 mg bid.

One of the most encouraging phase II studies was performed in patients with inoperable gastric carcinoma [14]. In this study, 14 patients received marimastat at a dose of 50 mg bid for 28 days. Endoscopic examination and biopsy were performed at entry and after 4 weeks of therapy. Continuation of marimastat was permitted if there was no endoscopic evidence of progression. Dose reduction to 25 mg od was necessary in eight patients because of severe musculoskeletal side effects; seven patients showed no evidence of progression and continued to receive marimastat beyond 28 days. There was macroscopic and histological evidence of biological activity in one patient, where a decrease in tumor cellularity and an increase in stromal tissue were observed over 7 months of treatment. Macroscopic changes consistent with stromal formation were also observed in three other patients. This has led to an ongoing phase III study examining the role of marimastat either alone or following response to chemotherapy in patients with inoperable gastric carcinoma. The main endpoint of the trial is survival and recruitment should be completed by December 1998.

Combination studies with chemotherapy have been performed and have demonstrated that coadministration of carboplatin and marimastat in patients with advanced ovarian cancer [1] and marimastat and gemcitabine in pancreatic cancer [6] is tolerable and safe. In the study utilizing gemcitabine in nonresectable pancreatic cancer, gemcitabine was administered at a dose of 1000 mg/m^2 weekly for 3 of every 4 weeks for a total of six cycles. Single-agent marimastat was coadministered continuously at sequential doses of 5, 10, 15, and 20 mg bid. A total of 31 patients were enrolled and the combination therapy was well tolerated: there did not appear to be any increase in the incidence or severity of chemotherapy-related adverse events nor did the combination increase the incidence of marimastat-related toxicities. Three patients achieved a partial response by radiological criteria and 18 had stable disease over three cycles; 10 had stable disease after six cycles of treatment. There was a fall in CA19-9 marker levels in 14 patients who received ≥4 cycles of treatment. The median survival time for this combination was encouraging at 9.7 months and, as a result, a large multinational randomized, double-blind, placebo-controlled phase III trial was initiated to determine whether marimastat improves quality of life and survival in patients with advanced disease who receive gemcitabine. This trial completed accrual in early 1998 and results should be available during 1999.

Summary and future developments

A large amount of preclinical data suggests that marimastat and other MMPIs could have an important role in the treatment of malignancy. Studies to date indicate that marimastat can be safely administered either alone or in combination with chemotherapy, although dose-limiting side effects of arthralgia and myalgia occur with unacceptable frequency at doses >25 mg daily. Toxicity is generally mild and manageable at 10 mg bid, and this is the regimen which is being used in all the pivotal studies. Encouraging data from phase II studies, particularly in gastric cancer, suggest that marimastat may have biological activity which reduces tumor growth, but firm evidence of an effect on clinical outcome is still not available.

The focus of current trials is to establish whether this agent improves the progression-free interval and survival in a variety of malignancies. It seems unlikely that significant tumor volume reduction (equivalent to partial or complete responses which are used to measure the activity of cytotoxic chemotherapy) will occur as a result of exposure to an MMPI. Even if reduction in tumor volume occurs, it may not be visualized using conventional imaging techniques due to the fibrosis which can be induced by these agents. However, preclinical experience suggests that a reduction in the rate of growth and metastasis of established disease can be expected; this would translate into a delay in the time to progression and prolonged survival. The adjuvant setting, when marimastat is given after all macroscopic disease has been removed by surgery or chemotherapy, may be the ideal situation in which to see a significant effect.

For these reasons, the focus of development of marimastat is now its use in randomized placebo-controlled studies using time to progression, quality of life, and, most importantly, survival as the major endpoints. The main trials are in lung (small and non-small cell), gastric, ovarian, breast, and pancreatic cancers. Encouraging preclinical data have also resulted in a study in patients with gliomas. In almost all of these studies, marimastat is being used in the adjuvant setting or with chemotherapy.

The development of marimastat has been complex and trial design has been more challenging than for any previous agent used in oncology. A series of large studies are now underway (and some have been completed) so that answers regarding whether this agent has a role in the treatment of cancer in a variety of settings should soon be available. Enormous interest has been generated by these studies and the results are eagerly awaited by basic scientists and clinicians alike. If survival duration is significantly increased, the prolonged administration of marimastat following the induction of remission of many tumors could provide a great advance in the management of malignancy.

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