SciMedCentral

Clinical Journal of Heart Diseases

Research Article

Antihypertensive Medications Can Prevent Fostamatinib-Induced Blood Pressure Elevation

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Submitted: January 08, 2024

Accepted: January 21, 2024

Published: January 24, 2024

ISSN: 2641-7766

Keywords

• Blood pressure; Fostamatinib; Nifedipine

Abstract

Fostamatinib is a tyrosine kinase inhibitor that has been shown in clinical trials to be effective against spleen tyrosine kinase in patients suffering from rheumatoid arthritis. Fostamatinib medication was linked in clinical trials to a slight increase in systemic arterial Blood Pressure (BP). This observation is consistent with other kinase inhibitors, particularly those that obstruct VEGFR2 signaling. In conscious rats, we examined the relationship between the elevation of blood pressure caused by fostamatinib and the plasma levels of the fostamatinib-active metabolite R940406. We discovered that there was a strong correlation between changes in R940406 plasma concentration and the time course of the blood pressure effect, suggesting a direct pharmacological relationship. The experiments yielded free plasma levels of R940406 up to 346 nmol/L, which is greater than the mean peak free plasma concentration of 49 nmol/L that has been recorded in clinical settings. We beyond the clinically noted mean peak free plasma concentration of 49 nmol/L, up to 346 nmol/L. We've shown that there are several effective ways to reduce the blood pressure elevation caused by fostamatinib dosing, including simple drug withdrawal or condoning with a variety of common antihypertensive medications like atenolol, captopril, and nifedipine. These results provide credence to prospective strategies for preserving patient safety during fostamatinib therapy. Additionally, we have shown—using nifedipine as an example drug—that this blood pressure control was not brought about by a decrease in R940406's plasma exposure, indicating that potential pharmacological benefits of the investigational drug may be preserved while blood pressure control is managed with the use of conventional medications.

INTRODUCTION

Phase III clinical development for patients with Rheumatoid Arthritis (RA) has been completed by fostamatinib (the prodrug of the active metabolite R940406, also known as R406), a small molecule oral kinase inhibitor with activity for Spleen Receptor Tyrosine Kinase (SYK). Phase III clinical studies are currently being conducted for patients with Immune Thrombocytopenia (ITP) (http://www.rigel.com/rigel/pipeline). Fostamatinib may prevent important stages in the development of autoimmune illness because it suppresses SYK-mediated immunological signaling in a variety of cell types implicated in inflammation and tissue damage [1]. Fostamatinib inhibits kinases other than the intended primary target, as is typical for receptor tyrosine kinase inhibitors (RTKi), as determined by isolated enzyme assays [2,3]. Fostamatinib (the prodrug of the active metabolite R940406, also referred to as R406) is a small molecule oral kinase inhibitor with activity for Spleen Receptor Tyrosine Kinase (SYK), has completed phase III clinical development for patients with Rheumatoid Arthritis (RA) [4] and is under investigation in phase III clinical studies for patients with Immune Thrombocytopenia (ITP) (http://www.rigel.com/rigel/pipeline). Fostamatinib inhibits SYK-mediated immune signaling in multiple cell types involved in inflammation and tissue damage and so may inhibit key steps in the progression of autoimmune disease [1,5]. As is common for Receptor Tyrosine Kinase Inhibitors (RTKi), fostamatinib inhibits kinases other than the intended primary target, when assessed in isolated enzyme assays [2,3]. Fosteramatinib consistently raised blood pressure in a manner comparable to what was seen in the phase II and III trials, according to a study that measured ambulatory blood pressure over the course of 24 hours in RA patients [6]. The theory that the rise in blood pressure may be directly related to the drug's pharmacology rather than being a reaction to another initiating effect is supported by the lack of evidence, if any, of any related side effects that may precede hypertensive changes (such as inhibition of renal function). Since kinase inhibitors like R940406 are relatively new, studying oncology trials where these drugs have been most successfully used may help us better understand the evolving efficacy and adverse effect profiles in particular thorough clinical and preclinical investigation. These preclinical supportive evidence and cancer trials teach us that cardiovascular alterations are a common observation in patients receiving experimental medications that target different kinase signaling pathways [7,8]. When combined with other anticancer medications that have known risks for cardiotoxicity, well-known medications like trastuzumab (Herceptin), a monoclonal antibody licensed for use against certain forms of breast cancer and targeted against mutant forms of the HER2/neu receptor, are linked to cardiac depression and an increased risk of unfavorable

outcomes [9]. Some kinase signaling inhibitor strategies, particularly those that block vascular endothelial growth factor, are linked to peripheral vascular effects, even if drugs like trastuzumab have direct cardiotoxic potential. The VEGFR2 receptor facilitates (VEGF) signaling [10]. From the fostamatinib trials, the second type of kinase inhibitor-induced cardiovascular side effect seems to fit the data the best. All of these approved anti-VEGF medications and experimental medications have been linked to cases of hypertension brought on by elevated peripheral resistance as a result of vascular constriction. This finding holds true irrespective of the location or mode of signaling inhibition, manifesting following administration of drugs that specifically target the circulating VEGF ligand, such as bevacizumab (Avastin) (analyzed by Syrigos KN, et al. [11] or the receptor's kinase signaling domain, like sunitinib (Sutent) [12] and cedirinib (Recentin) [13]. According to Shah DR, et al. [14], hypertension is currently recognized as a proven class impact of the VEGF inhibitor class al. 2013), in addition to the fact that it is increasingly believed to have potential as a biomarker to predict a positive efficacy outcome for various dose levels of some drugs in the class, such as axitinib [15], sunitinib [16] and bevacizumab [17]; Scartozzi M, et al. [18]. The most frequently suggested and accepted mechanism for the hypertension caused by the inhibition of VEGF signaling [19] is an increase in peripheral vascular resistance that occurs after endothelial Nitric Oxide Synthase (eNOS) physiological relaxant activities are inhibited. Based on this knowledge, several clinical protocols have been developed to manage hypertension after anti-VEGF treatments to preserve the safety of the patients [20]. These safety monitoring and intervention plans include using a variety of common antihypertensive medications, reducing dosages, and stopping treatment if specific hypertension levels are seen. The objective of the research presented here was to examine the pharmacodynamics and dynamics of fostamatinib-induced rise of blood pressure in preclinical models and to determine whether these findings were consistent or different from those of anti-VEGF drugs. Secondly, the potential of antihypertensive drugs with varying methods to regulate fostamatinib-induced alterations in blood pressure was examined, building on the knowledge and handling of blood pressure attenuation with VEGF inhibitors in both nonclinical models and clinical settings (Figure 1).

MATERIALS AND METHODS

In each experiment, male Sprague Dawley rats weighing between 250 and 300 g were surgically implanted under pentobarbital anesthesia at Charles River Laboratories (Raleigh, NC) or at AstraZeneca Alderley Park (Macclesfield, Cheshire, UK) with TL11M2-C50- PXT telemetry transmitters (Data Sciences International, St. Paul, MN). To eliminate the little variations in blood pressure linked to the estrous cycle, male rats were chosen. The peritoneal implantation of the transmitter and an abdominal midline incision comprised the sterile surgical procedure. The pressure cannula was placed with its tip resting about 1 cm caudal to the left renal artery's emergence, rostral to the aortic bifurcation. Research were categorized as chronic, lasting 28 days, or acute, lasting more than one week in the live phase. Rats received complete advertisement exposure during a 12-hour light-dark cycle. Ad libitum access to home potable water and a regular rat food (Purina Labdiet 5001). Fostamatinib was supplied orally in quantities of 10 mL/kg using an aqueous solution containing 0.1% sodium carboxymethylcellulose, 0.1% methyl paraben, and 0.02% propyl paraben in all investigations. Using Dataquest A.R.T. software (Data Sciences International), 30-second samplings were taken every five minutes to create all of the telemetry recordings. Rats utilized in trials with automated blood sampling were again put under anesthesia with pentobarbital and surgically implanted with a femoral vein cannula, advanced 45 mm into the inferior vena cava, after a two-week recuperation time at the vendor following the implantation of the telemetry device. During the study's experimental phase, the cannula was utilized to draw blood samples utilizing a blood sample that is automated (Culex, BASi, West Lafayette, IN). After that, rats were transported to AstraZeneca, where they spent a week getting used to the surroundings before being attached to the Culex automatic blood sampler. An extra 16 hours were allocated for acclimatization prior to the start of the experimental phase.

28 days dosing study

24 male Sprague Dawley rats were given two daily oral doses of either vehicle or fostamatinib (8.5 or 30 mg/kg) for a total of 28 days in order to determine the time course and reversibility of fostamatinib-induced increases in blood pressure after 28 days of repeat dosing. The first dose of each day was given at around 8 AM, and the second dose at about 2 PM. These study rats were dosed with a fake vehicle for three days prior to this regimen to help them become used to the process. On day twelve of the trial, plasma concentrations of the active fostamatinib metabolite, R940406, were measured. In order to acquire steady-state minimum and maximum typical exposures, each rat was bled via a tail vein before to the first daily dose and two hours after the second daily dosage for every rat. To ensure that the hypertensive effects might be reversed, telemetry recording was maintained for three weeks following the end of the dosage. The test substances were taken orally. Day 1 saw the administration of the vehicle (1% polysorbate, p.o.) at a dosage amount of 5 mL/kg. For a full day, cardiovascular data were obtained. Day 2: Using a dosage volume of 5 mL/kg, fostamatinib (100 mg/kg p.o.) was given, and cardiovascular data were once more recorded for up to 48 hours (this was to allow monitoring of any recovery phase).

Antihypertensive combination studies

Four separate investigations, with a minimum 2-week interval between treatment levels for any animals used more than once, were conducted at Alderley Park, UK, in groups of four Han Wistar rats from a colony of 16 rats implanted with radiotelemetry devices as previously described. For the two days that followed this (i.e., the days after compound dose), more data were collected in order to measure any necessary recovery phases. Based on the antihypertensive medicines'

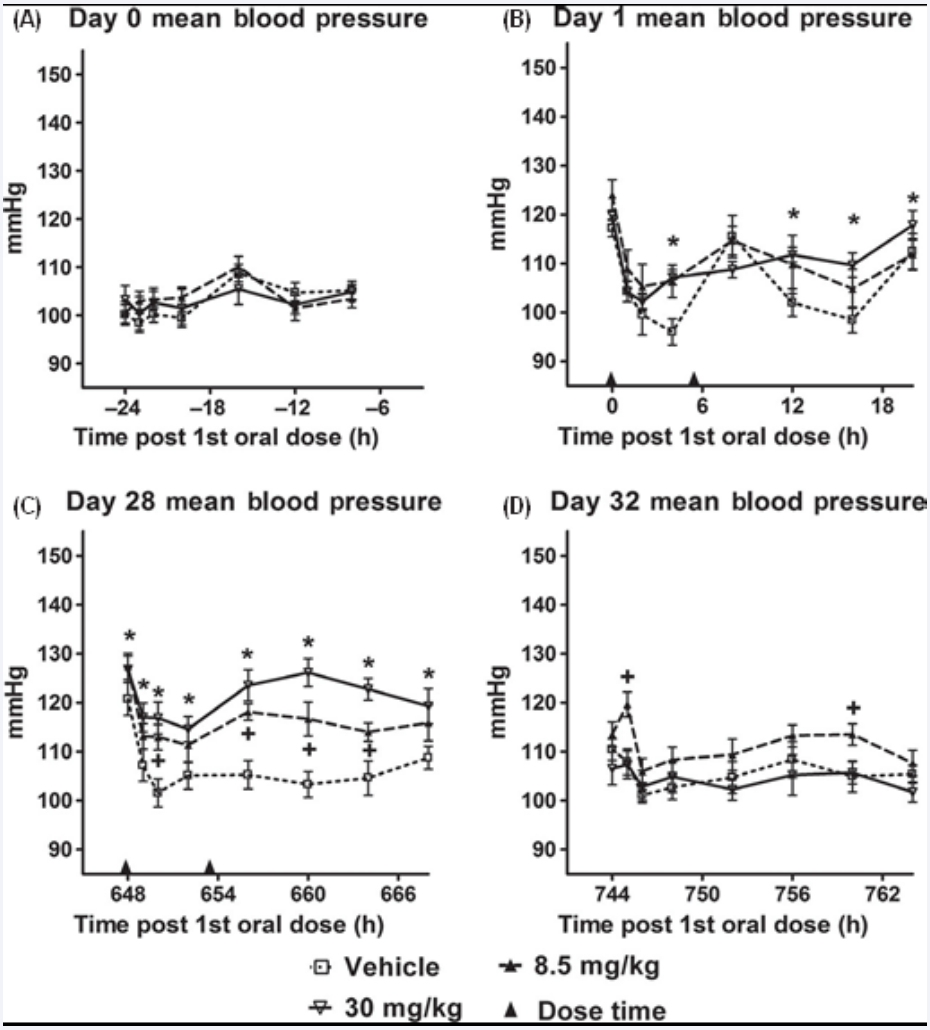

Figure 1 Time courses of fostamatinib-induced elevations in mean arterial blood pressure on select days of the study. After basal blood pressure was measured on day 0 (A), bid dosing began on day 1 (B), and ended on day 28 (C). Significant changes produced by 8.5 mg/kg fostamatinib from time-matched vehicle treatment, +P < 0.05. Significant changes produced by 30 mg/kg fostamatinib from time-matched vehicle treatment,*P < 0.05. A return to baseline after cessation of dosing was noted (D). All groups contained eight rats.

anticipated pharmacokinetics in rats, the timing of their dose in relation to the fostamatinib administration was logically chosen in the experiments. Each administration's schedule was planned to evaluate how well it might control the anticipated peak hypertensive effect following fostamatinib dosage. Captopril's comparatively sluggish absorption but extended the rat's plasma cover time, and it was administered two hours before the fostamatinib. Both nifedipine and atenolol were dosed 30 minutes or 2 hours after fostamatinib, respectively. However, nifedipine's shorter duration of action is attributed to its faster plasma clearance. Following Twenty-four additional rats were used in this study. On the experimental day rats received one of four possible dosing regimens. All rats received two oral dosing of 10 mL/kg each, with each volume contain in gam appropriate volume of either the vehicle or the vehicle plus 100 mg/kg of fostamatinib or the vehicle plus 2 mg/kg of nifedipine. The two dosing were separated by a 2-hperiod. The dose groups were as follows: Group I – fostamatinib at time 0; Group II – fostamatinib and nifedipine at time 0; Group III – nifedipine at time 0; Group IV –fostamatinib at time 0 and nifedipine 2 h later. Plasma concentrations of R940406, the active fostamatinib metabolite, were obtained from each telemetered rat via the automated blood sampler at 1, 3, 4, 8, 9, 10, 11, 12, 16, 24, and 48 h after the first oral dose of the study dosing of the VEGFR2 kinase inhibitor carinaria, the dosages of each chemical were chosen based on previously established antihypertensive efficacy [21]. The doses for captopril, atenolol, and nifedipine were 10 mg/kg, 15 mg/kg, and 30 mg/kg, respectively. The antihypertensive medications were administered orally via gavage with a 1% polysorbate vehicle at a dosage volume of 0.25 mL/100 g Sampler at 1, 3, 4, 8, 9, 10, 11, 12, 16, 24, and 48 hours following the study's initial oral dosage.

Statistical analyses

Two-way t-tests were used in all studies to compare baselines before dosage. The mean level at each timepoint was chosen as the main effect measure. It is conceivable for compound effects to result in increases or declines from the vehicle, which calls for a two-sided testing strategy. Variations from the vehicle are shown with the corresponding standard errors (as variations in the least squares means). If the P-value is less than 0.05, the effects are considered statistically significant (at the 5% level). Unsupported by comparable changes at other time-points, higher dosages, or other relevant parameters, isolated significant differences (e.g., one or two timepoints at one dose in a parameter) would typically not be regarded meaningful effects; no correction for multiple testing was made. A model of random effects is fitted using a variance-components covariance pattern, animal fitted as random, and the Kenward-Roger approach [22] for determining degrees of freedom. Categorical variables are fitted using the group and time-point. Fitting is also done for the two-way interaction between these parameters. When there are no missing data, the reported least squares means [23] are the same as the arithmetic means. The technique uses the fact that each animal is measured multiple times to yield a more reliable estimate of the standard error of the mean changes.

Fostamatinib's effect on blood pressure was investigated in telemetered rats through a 28-day dosing study. Special attention was paid to the changes that occurred immediately following the first dose, any changes that continued to develop after the 28-day period, and the resolution of these effects a few days after the dose was finished. Telemetered rats given oral fostamatinib at doses of 8.5 mg/kg and 30 mg/kg twice a day showed higher mean arterial blood pressure than the vehicle-controlled comparator group. Regarding the degree of change and time to onset, there was a discernible difference between the two dose levels' results; the 30 mg/kg group saw a larger elevation of blood pressure and a quicker onset to the animals treated with 8.5 mg/kg less. Throughout the 28 days of daily dosing of fostamatinib, the mean, systolic, and diastolic arterial pressures increased gradually by degree and duration for both the high dose (30 mg/kg) and the low dose (8.5 mg/kg) displays representative mean blood pressure data. After the second dose on day 1, a significant and prolonged rise in blood pressure was brought on by the 30 mg/kg dose. After administering 8.5 mg/kg, blood pressure did not rise statistically significantly until about day 14, and by day 28, this increase had persisted, with systolic pressure rising more than with vehicle therapy. R940406's total minimum plasma concentrations measured that day For the 8.5 and 30 mg/kg treatment groups, the values 12 hours before the first daily fostamatinib dose were 0.067 ~ 0.025 and 0.584 ~ 0.125 lmol/L, respectively. The highest values recorded two hours following the second daily dosage were 1.27 ~ 0.45 and 5.05 ~ 2.96 lmol/L for the treatment groups receiving 8.5 and 30 mg/kg, respectively. This indicated that the dosages of 8.5 and 30 mg/kg were causing dose-related increases and decreases in plasma exposure. Using an estimate of 97.9% plasma protein binding for R940406 in the rat, these total levels at 2 hours indicate free levels of 27 to 106 nmol/L, which compares well to a clinical mean peak free plasma concentration observed in trials of roughly 49 nmol/L. These plasma levels coincide with the 33–158 nmol/L previously reported in vitro IC50 values for in both rat and human immune cells, R940406-induced suppression of certain SYK-dependent cellular activities (Rolf, Curwen, Veldman-Jones, Eberlein, Wang, Harmer, Hellawell and Braddock, in press). Moreover, R940406 has been demonstrated to suppress VEGF-driven endothelial tube formation in vitro in a cellular assay within the range of 10–300 nmol/L, which is in agreement with these plasma exposures (Rolf et al. in prep.). On day 32, or four days after the dosage was stopped, the rises in blood pressure brought on by both fostamatinib doses seemed to have disappeared. There were just a few statistically significant blood pressure readings on this particular day.

Intervention studies using nifedipine with automated blood sampling

Oral nifedipine treatment inhibited the coadministration of fostamatinib at a dose of 100 mg/kg in Sprague Dawley rats, resulting in a 10-17% increase in mean arterial blood pressure. This effect was reversed when the medication was administered two hours later. Eight hours after the first fostamatinib dose, the effects of nifedipine started to fade four hours into the fostamatinib treatment, finally allowing the fostamatinib-induced increase of blood pressure to reappear. The average measured peak plasma levels of R940406 were similar to those obtained during the initial acute single dose study and equivalent across all treatment groups administered fostamatinib. This suggests that nifedipine co dosing was not reducing the rats' effective exposure to R940406 and that changes in blood pressure elevation during combination phases of studies were occurring were not brought on by modifications in pharmacokinetics.

DISCUSSION AND CONCLUSION

We have shown that the rises in blood pressure seen in fostamatinib clinical trials can be repeated in rat preclinical investigations. Following a single oral dose of fostamatinib in rats, blood pressure has been shown in previous studies to increase with little to no delay in relation to the build-up of the active molecule R940406 in plasma, especially when using doses above 30 mg/kg. However, in a more chronic 28-day dosing study, lower doses cause a gradual rise in baseline at some point between 1 and 28 days, which may be explained by increased plasma exposure with subsequent daily doses. When single doses are matched in studies with pharmacokinetic measurements, there is an abrupt spike and decrease in blood pressure with relation to baseline the initiation and resolution of the R940406 plasma concentration pattern, indicating a direct causative link as previously reported. According to our data, plasma concentrations as high as 16 lmol/L do not cause a further rise in blood pressure in conscious rats, although they do have a maximum hypertensive effect of about 15 mmHg. The previous finding in our work that homeostatic control of any greater blood pressure increase in the rat is very efficient, likely explains this

lack of a proportionate relationship at the higher concentrations. As a result, there is a physiological limit to the degree of blood pressure change that can be induced and measured due to the onset of reflex settlement [21]. The resolution of an established blood pressure increase in the chronic study after stopping dosing on day 28 and returning to nearly the original baseline on the next measure at day 32 argues against a permanent underlying change in the animal once drug is withdrawn, in a manner similar to how blood pressure rises being related to plasma levels of R940406 in an acute setting after a single dose. When considered collectively, and controlling for rat reflex control, the data indicate a straightforward, dynamic relationship—free of induction or lag periods—between blood pressure and R940406 plasma levels. The correlation between the level of circulating active medication and the rise in blood pressure provides mechanistic evidence for certain clinical observations clinically appropriate plans for mitigation and management. A consideration of timing alone argues against the need to identify involvement of other causal side effects, such as the highly unlikely scenario in which the effect results from ongoing renal impairment leading to a rise in blood pressure following volume loading over time. This is because there is no induction period between drug exposure and the rat's beginning of the blood pressure rise. Crucially, since there doesn't seem to be a long-term correlation between drugs and blood pressure, drug withdrawal in patients whose blood pressure rise may need to be regulated should provide a return to pretreatment levels after drug clearance high blood pressure drive. While a strong and repeatable relationship between plasma levels of a prohypertensive kinase inhibitor and an increase in blood pressure can be established in healthy inbred rat strains, clinical learning from the oncology field indicates that patients are known to exhibit much greater variability [14]. Patients, especially the elderly population with inflammatory autoimmune disease, have a greater diversity of cardiovascular health and homeostatic capability. Therefore, for a given plasma level of R940406, patients may exhibit no change in blood pressure or a relatively large change depending on the ability of their physiological reflexes to compensate. Therefore, while knowledge of preclinical pharmacokinetics may be able to offer a helpful forecast of a change in blood pressure in any individual as the data shows, these relationships may hold true for a wide population of patients because variations will eventually average out. However, one should not anticipate that the level of a drug in the blood can be used to accurately predict the degree of blood pressure change that is observed on an individual basis. Based on in vitro cell studies, the plasma levels of R940406 that were linked to BP alterations in this investigation are adequate to match the amounts that would be predicted to suppress VEGF signaling (Rolf et al. in prep.). Furthermore, additional prior in vivo mechanistic research has demonstrated that the blood pressure increases brought on by R940406 are in line with those brought on by substances that specifically block VEGF signaling. Based on the preclinical experience of controlling hypertension resulting from the administration of cediranib, a potent VEGF receptor kinase inhibitor [21], we were able to show in this series of investigations that the rat's fostamatinib-induced hypertension could be effectively controlled with conventional antihypertensive drugs of various classes. Regardless of the antihypertensive mechanism, there was no evidence of resistance to any of the medications examined, suggesting that the majority of patients will likely benefit from the same techniques in the clinic. These findings support the management of elevated blood pressure in RA patients on fostamatinib and receiving blood pressure management from a range of medications that targetvarying systems. Remembering that there are differences in cardiovascular health and homeostatic capability within a clinical population should be taken into account as part of a safety management plan for blood pressure increases and the selection of antihypertensive therapy for an agent like fostamatinib. This was covered above in the context of the relationship between drug level and blood pressure increase in an individual patient. Certain antihypertensive medications work by interfering with homeostatic processes. Captopril, for instance, inhibits the Angiotensin-Converting Enzyme (ACE) to lessen the production of vasoconstrictive angiotensin II from angiotensin I. Angiotensin II may already be physiologically downregulated in a patient with pre-existing hypertension by reflex suppression of renin creation. Because there would be less angiotensin II tone in these patients, captopril would not have the predicted blood pressure-lowering effect. It has been demonstrated earlier that certain antihypertensive medications do not work as well against blood pressure increases caused by VEGF inhibitors if the dose level exceeds the tested rats' reflex capacity [21]. However, under these circumstances, we have shown that the use of agents—like the calcium channel blocker nifedipine-that do not depend on regular homeostatic mechanisms can nonetheless normalize blood pressure. Fosteramatinib's significantly lesser blood pressure-lowering effect shown in the clinic thus far suggests that patients may frequently become resistant to several antihypertensive medication classes on therapy, possibly only observed in the most severely affected patients, necessitating a change to a more directly acting medication; however, the pattern of antihypertensive drug effectiveness should remain the same. Nifedipine was selected as an example antihypertensive agent in these studies to examine drug–drug interactions because of its potential benefits. We showed that the agent's ability to reduce fostamatinib-induced blood pressure increases was not caused by changing the levels of R940406 in plasma. These findings showed that the intended antihypertensive mechanism of nifedipine was responsible for the normalization of blood pressure, and secondly, that the usage of medications such as nifedipine can still maintain baseline blood pressure in the presence of R940406 at therapeutically effective concentrations. In conclusion, we have demonstrated that fostamatinib causes a rise in blood pressure in rats that is directly correlated with its exposure to plasma and that, over time, a simple medication withdrawal is enough to bring the rat's blood pressure back to normal. Moreover, we have shown that a variety of conventional antihypertensive medications can stop or reverse the rise in blood pressure. With this knowledge, we suggest that the blood pressure control strategies used in VEGF signaling inhibitor

oncology trials could be applied to fostamatinib trials as well, even though the observed effects were much smaller than those reported in the oncology setting. This involves using an approach that is sequential, starting with the use of antihypertensive medications of any kind and then switching to an agent like as nifedipine in cases where patients are not responding to the first treatments; drug discontinuation is a useful supplementary treatment.

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