



## Pazopanib

Updated: July 12, 2014.

## OVERVIEW

### Introduction

Pazopanib is a multi-kinase inhibitor active against vascular endothelial growth factor receptors-1, -2 and -3 that is used in the therapy of advanced renal cell carcinoma and soft tissue sarcomas. Pazopanib therapy is commonly associated with transient elevations in serum aminotransferase during therapy and has been linked to rare, but occasionally severe and even fatal cases of clinically apparent acute liver injury.

### Background

Pazopanib (paz oh' pa nib) is an orally available, multi-kinase inhibitor, most potently inhibiting the tyrosine kinase receptors of vascular endothelial growth factor (VEGF) 1, 2 and 3 which are associated with tumor growth and angiogenesis. Pazopanib also has activity against c-KIT (an abnormal tyrosine kinase found in gastrointestinal stromal tumors) and the platelet derived growth factor (PDGF) receptor. Clinical trials of pazopanib in malignant diseases in humans have shown activity against renal cell carcinoma and soft tissue sarcoma and promising effects in ovarian and thyroid cancer. Pazopanib received approval for use in the United States in 2012 and current indications include advanced renal cell cancer and soft tissue sarcomas. Pazopanib is available in tablets of 200 and 400 mg under the brand name Votrient. The typical dose is 800 mg once daily. Lower doses are recommended for patients with moderate-to-severe liver disease (200 mg daily) and the dose can be reduced to 400 mg daily for toxicity. Common side effects include fatigue, diarrhea, hypertension, hair color changes, anorexia, nausea, and bone marrow suppression. Uncommon, but potentially severe side effects include prolonged QTc intervals, hemorrhages, arterial thrombosis and visceral perforations and fistulae.

### Hepatotoxicity

In large clinical trials, abnormalities in routine liver tests were common in patients treated with pazopanib, with serum aminotransferase elevations occurring in up to half of patients and total serum bilirubin in approximately one-third. ALT and AST values greater than 5 times the upper limit of normal (ULN) occurred in 8% of patients and combinations of ALT and bilirubin elevations in 1% to 2%. In preliminary trials of pazopanib in various solid tumors, there were rare reports of hepatitis with jaundice in <1% of patients. Subsequently, fatal instances of liver injury have been reported and the clinical features of the hepatotoxicity have been better defined. The clinical onset is typically within 4 to 12 weeks of starting pazopanib and the pattern of serum enzyme elevations is usually mixed. Immunoallergic and autoimmune features are not present. The course is typically self-limited, but can be prolonged and severe and fatal instances have been reported (Case 1).

## Mechanism of Injury

The mechanism of injury accounting for serum enzyme elevations during pazopanib therapy is not known. Retrospective analyses and genetic studies have suggested that other medications (simvastatin) and HFE polymorphisms may play a role in serum aminotransferase elevations and Gilbert syndrome in hyperbilirubinemia. Pazopanib is metabolized in the liver largely through the CYP 3A4 pathway and liver injury may be related to production of a toxic intermediate. Pazopanib is susceptible to drug-drug interactions with agents that inhibit or induce hepatic CYP 3A4 activity.

## Outcome and Management

Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) or any elevations accompanied by jaundice or symptoms should lead to dose reduction or temporary cessation. There does not appear to be cross reactivity in risk for hepatic injury between pazopanib and other kinase inhibitors and, in some situations, switching to another tyrosine kinase receptor inhibitor may be appropriate.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

## CASE REPORT

### Case 1. Severe acute liver injury and hepatic failure due to pazopanib.

[Modified from: Klempner SJ, Choueiri TK, Yee E, Doyle LA, Schuppan D, Atkins MB. Severe pazopanib-induced hepatotoxicity: clinical and histologic course in two patients. *J Clin Oncol* 2012; 30: e264-8. [PubMed Citation](#)]

A 77 year old man with metastatic renal cell carcinoma developed jaundice 6 weeks after starting pazopanib (800 mg daily). He had no previous history of liver disease and had normal routine liver tests before therapy and after 2 weeks of treatment (Table). He had no risk factors for viral hepatitis or history of alcohol abuse and was taking no other potentially hepatotoxic medications. On presentation, serum bilirubin was 6.3 mg/dL, ALT 759 U/L, AST 296 U/L and alkaline phosphatase 729 U/L. Pazopanib was stopped promptly and he was monitored closely. Tests for viral hepatitis A, B and C and cytomegalovirus infection were negative as were routine autoantibodies. A liver biopsy showed acute cholestatic hepatitis with mild bile duct injury. While serum aminotransferase levels rapidly fell to near normal levels, serum alkaline phosphatase remained high and bilirubin levels rose. Four weeks after presentation, the prothrombin time began to rise and the patient died of hepatic failure approximately 9 weeks after initial presentation.

### Key Points

Medication:	Pazopanib (800 mg daily)
Pattern:	Mixed (R~3: normal values not provided)
Severity:	5+ (hepatic failure and death)
Latency:	6 weeks
Recovery:	None
Other medications:	None mentioned

## Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre	Pre	25	100	0.2	
0	Pre	22	98	0.2	Pazopanib started
2 weeks	Pre	30	89	0.3	INR 1.1
6 weeks	0	759	729	6.3	Pazopanib stopped
7 weeks	1	166	523	10.4	INR 1.1
8 weeks	2 weeks	55	426	15.7	Liver biopsy
9 weeks	3 weeks	38	381	22.9	
10 weeks	4 weeks	34	437	18.6	INR 1.8
11 weeks	5 weeks	29	484	14.9	INR 1.7
15 weeks	9 weeks	28	484	13.0	Death
<b>Normal Values</b>		<b>Not given</b>	<b>Not given</b>	<b>&lt;1.2</b>	

## Comment

Elevations in serum aminotransferase levels occur in up to 50% of patients treated with pazopanib and rise to above 5 times ULN (approximately 200 U/L) in 8% of patients. Regular monitoring of liver tests is recommended. In this patient, monitoring of liver enzymes was done, but he presented with clinically apparent liver injury despite such monitoring and progressed to hepatic failure despite prompt discontinuation of therapy. The initial pattern of liver enzyme elevations was mixed, with prominent elevations in both serum aminotransferase and alkaline phosphatase levels. Subsequently, serum ALT levels fell, but alkaline phosphatase levels remained high and bilirubin levels continued to rise. A liver biopsy was done that reportedly showed active cholestatic hepatitis with some degree of bile duct injury and ductular proliferation. Within a few weeks, signs of hepatic failure arose and the patient died 9 weeks after presentation with what might be considered a subacute hepatic failure. The patient's age and other comorbidities may have contributed to the poor outcome. A second patient (62 year old man) described in this report had a similar presentation with a mixed pattern of serum enzymes (ALT 935 U/L, Alk P 784 U/L) and jaundice (bilirubin 3.7 mg/dL), but had spontaneous improvement starting 3 weeks after stopping pazopanib and ultimate complete recovery.

## PRODUCT INFORMATION

### REPRESENTATIVE TRADE NAMES

Pazopanib – Votrient®

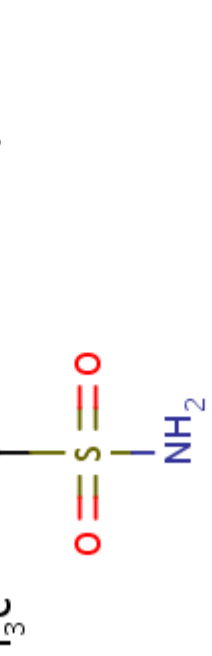
### DRUG CLASS

Antineoplastic Agents

### COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

## CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Pazopanib	444731-52-6	C <sub>21</sub> -H <sub>23</sub> -N <sub>7</sub> -O <sub>2</sub> -S	 <p>The chemical structure of Pazopanib is a complex organic molecule. It features a central benzimidazole ring system. One of the nitrogen atoms in the benzimidazole is substituted with a methyl group (CH<sub>3</sub>). The benzimidazole is connected via its 2-position to a pyridine ring. The pyridine ring is further substituted at its 3-position with a methylamino group (-NH-CH<sub>3</sub>). The pyridine ring is also connected via its 4-position to a benzene ring. This benzene ring has a methyl group (H<sub>3</sub>C) at the 2-position and a sulfonamide group (-SO<sub>2</sub>NH<sub>2</sub>) at the 3-position. The sulfonamide group is shown with two oxygen atoms (O) and one nitrogen atom (NH<sub>2</sub>).</p>

## ANNOTATED BIBLIOGRAPHY

References updated: 12 July 2014

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

*(Review of hepatotoxicity published in 1999 before the availability of tyrosine kinase inhibitors such as pazopanib).*

DeLeve LD. Erlotinib. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 556.

*(Review of hepatotoxicity of cancer chemotherapeutic agents discusses several tyrosine kinase inhibitors including imatinib, gefitinib, erlotinib and crizotinib, but not pazopanib).*

Chabner BA, Barnes J, Neal J, Olson E, Mujagic H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-54.

*(Textbook of pharmacology and therapeutics).*

Sleijfer S, Ray-Coquard I, Papai Z, Le Cesne A, Scurr M, Schöki P, Collin F, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol 2009; 27 (19): 3126-32. PubMed PMID: 19451427.

*(Among 142 patients with advanced soft tissue sarcomas, pazopanib demonstrated "interesting activity" and side effects included anemia [75%], leucopenia [42%], thrombocytopenia [10%], hypertension [40%], fatigue [37%], diarrhea [30%], nausea [36%], and elevations in ALT [50%], bilirubin [38%] and creatinine [26%]).*

Xu CF, Reck BH, Xue Z, Huang L, Baker KL, Chen M, Chen EP, et al. Pazopanib-induced hyperbilirubinemia is associated with Gilbert's syndrome UGT1A1 polymorphism. Br J Cancer 2010; 102: 1371-7. PubMed PMID: 20389299.

*(Among 246 patients with cancer treated with pazopanib, analysis of genetic polymorphisms of 11 candidate genes found an association of hyperbilirubinemia with the gene for Gilbert syndrome).*

Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios CH, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010; 28: 1061-8. PubMed PMID: 20100962.

*(Among 435 patients with advanced renal cell cancer, objective tumor responses occurred in 30% of pazopanib vs 3% of placebo recipients, but side effects were common including ALT increases in 53% [≥5 times ULN in 12%], diarrhea [52%], hypertension [40%], hair color change [38%], nausea [26%], thrombotic events [3%], and one patient died of hepatic failure).*

Everolimus and pazopanib: two new drugs for renal cell cancer. Med Lett Drugs Ther 2010; 2 (1337): 33-4. PubMed PMID: 20431519.

*(Concise summary of efficacy, safety and costs of pazopanib shortly after its approval for use in the US; mentions "the possibility of severe and fatal hepatotoxicity" and recommendation to monitor liver tests closely).*

Bukowski RM, Yasothan U, Kirkpatrick P. Pazopanib. Nat Rev Drug Discov 2010; 9: 17-8. PubMed PMID: 20043026.

*(Brief summary of history of development of pazopanib, its mechanism of action, clinical indications and place in "the market", mentions that pazopanib is associated with side effects of hepatic toxicity).*

Xu CF, Reck BH, Goodman VL, Xue Z, Huang L, Barnes MR, Koshy B, et al. Association of the hemochromatosis gene with pazopanib-induced transaminase elevation in renal cell carcinoma. *J Hepatol* 2011; 54: 1237-43. PubMed PMID: 21145803.

*(Analysis of 6852 genetic polymorphisms among 242 patients with cancer treated with pazopanib identified 92 polymorphisms in 40 genes associated with ALT elevations and focused upon two markers in the HFE gene).*

Keisner SV, Shah SR. Pazopanib: the newest tyrosine kinase inhibitor for the treatment of advanced or metastatic renal cell carcinoma. *Drugs* 2011; 71: 443-54. PubMed PMID: 21395357.

*(Review of mechanism of action, efficacy and safety of pazopanib therapy of renal cell cancer lists side effects including elevations in ALT in 53% of patients [ $\geq 5$  times ULN in 12%] and bilirubin in 36% [ $\geq 3$  times ULN in 4%]).*

Xu CF, Xue Z, Bing N, King KS, McCann LA, de Souza PL, Goodman VL, et al. Concomitant use of pazopanib and simvastatin increases the risk of transaminase elevations in patients with cancer. *Ann Oncol* 2012; 23: 2470-1. PubMed PMID: 22918879.

*(Retrospective analysis of ALT elevations [ $\geq 3$  times ULN] in 976 patients on pazopanib found higher rate in those also taking simvastatin [27%] and atorvastatin [17%] compared to those not on a statin [14%]).*

Klempner SJ, Choueiri TK, Yee E, Doyle LA, Schuppan D, Atkins MB. Severe pazopanib-induced hepatotoxicity: clinical and histologic course in two patients. *J Clin Oncol* 2012; 30: e264-8. PubMed PMID: 22802316.

*(Two patients, 77 and 62 year old men with renal cell cancer developed jaundice 4-6 weeks after starting pazopanib [peak bilirubin 22.9 and 4.5 mg/dL, ALT 759 and 935 U/L, Alk P 729 and 784 U/L], one dying of hepatic failure and one recovering within 3 months of stopping: Case 1).*

Motzer RJ, Johnson T, Choueiri TK, Deen KC, Xue Z, Pandite LN, Carpenter C, Xu CF. Hyperbilirubinemia in pazopanib- or sunitinib-treated patients in COMPARZ is associated with UGT1A1 polymorphisms. *Ann Oncol* 2013; 24: 2927-8. PubMed PMID: 24107802.

*(Among 1110 patients with renal cell cancer treated with tyrosine kinase inhibitors, bilirubin elevations  $\geq 1.5$  times ULN occurred in 16% on pazopanib vs 9% on sunitinib, and the accumulated rate of the elevations was higher in patients who were homozygous for the UGT1A1 polymorphisms of Gilbert syndrome).*

Shibata SI, Chung V, Synold TW, Longmate JA, Suttle AB, Ottesen LH, Lenz HJ, et al. Phase I study of pazopanib in patients with advanced solid tumors and hepatic dysfunction: a National Cancer Institute Organ Dysfunction Working Group study. *Clin Cancer Res* 2013; 19: 3631-9. PubMed PMID: 23653147.

*(Among 98 patients with advanced solid tumors and varying degrees of liver dysfunction treated with varying doses of pazopanib, found the poor tolerance of standard doses among patients with moderate-to-severe liver dysfunction was not due to decrease in drug clearance).*

Kapadia S, Hapani S, Choueiri TK, Wu S. Risk of liver toxicity with the angiogenesis inhibitor pazopanib in cancer patients. *Acta Oncol* 2013; 52: 1202-12. PubMed PMID: 23594201.

*(Systematic review of hepatic toxicity of pazopanib based upon 10 clinical trials with 1478 patients calculated rate of ALT elevations as 41% [ $\geq 5$  times ULN in 9%] and bilirubin 25% [ $\geq 3$  times ULN 3%], with only 2 cases of fatal hepatic failure).*

Spraggs CF, Xu CF, Hunt CM. Genetic characterization to improve interpretation and clinical management of hepatotoxicity caused by tyrosine kinase inhibitors. *Pharmacogenomics* 2013; 14: 541-54. PubMed PMID: 23556451.

*(Review of genetic associations of serum ALT and bilirubin elevations during therapy with tyrosine kinase inhibitors focusing on lapatinib and pazopanib).*

Shah RR, Morganroth J, Shah DR. Hepatotoxicity of tyrosine kinase inhibitors: clinical and regulatory perspectives. *Drug Saf* 2013; 36: 491-503. PubMed PMID: 23620168.

*(Review of the hepatotoxicity of 18 tyrosine kinase inhibitors approved for use in cancer in the US as of 2013 mentions that cases of acute hepatitis and fatal hepatic failure have been described in patients receiving pazopanib and that aminotransferase elevations occur in 46-53% of patients [  $\geq 5$  times ULN in 7-12%], generally within the first 18 weeks of treatment).*

Teo YL, Ho HK, Chan A. Risk of tyrosine kinase inhibitors-induced hepatotoxicity in cancer patients: a meta-analysis. *Cancer Treat Rev* 2013; 39: 199-206. PubMed PMID: 23099278.

Bible KC, Suman VJ, Molina JR, Smallridge RC, Maples WJ, Menefee ME, Rubin J, et al.; Endocrine Malignancies Disease Oriented Group, Mayo Clinic Cancer Center, and the Mayo Phase 2 Consortium. A multicenter phase 2 trial of pazopanib in metastatic and progressive medullary thyroid carcinoma: MC057H. *J Clin Endocrinol Metab* 2014; 99: 1687-93. PubMed PMID: 24606083.

*(Among 35 patients with advanced medullary thyroid cancer treated with pazopanib for 1-43 months, liver test abnormalities occurred in 6%).*

Karczmarek-Borowska B, Sałek-Zań A. Hepatotoxicity of molecular targeted therapy. *Contemp Oncol (Pozn)* 2015; 19: 87-92. PubMed PMID: 26034384.

*(Review of hepatotoxicity of modern molecular targeted therapies including monoclonal antibodies, protein kinase inhibitors and proteasome inhibitors; pazopanib has an increased risk of liver injury).*