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TYROSINE KINASE INHIBITORS IN PULMONARY VALSCULAR DISEASE

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What is an abnormal pulmonary pressure?

- **PHT defined as --- Mean PAP greater than:**

  25 mm Hg at rest

  30 mm Hg during exercise, by RT H cath

- **Normal ------ P AP (mm Hg):**

Systolic	**18 -25**
Diastolic	**6 -10**
Mean	**12 -16**
PCWP	**6 -10**
	20

Pathophysiology

- PAH is a disease of the small pulmonary arteries that involves a progressive and extensive vascular remodeling.
- Remodeling of the lung vasculature includes:
  - Medial hypertrophy
  - Muscularization of small arterioles
  - Intimal thickening
  - Formation of plexiform lesions.
- The remodeling process is the consequence of
  - Cellular hypertrophy
  - Hyperplasia
  - Inflammation
  - apoptosis, migration, and deposition of extracellular

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Pathophysiology

- These drugs target 3 different pathways:
  1- Prostacyclin (PGI2)
  2- Endothelin (ET-1)
  3- Nitric oxide (NO) .
- Clinical improvements achieved by these molecules are mainly mediated by vasodilator effects with a moderate effect on pulmonary vascular remodeling.
- Intense research is currently ongoing to discover potential new pathways involved in the pathogenesis of PAH and new therapeutic targets.
- Receptor tyrosine kinases (RTKs)are recently becoming one of these promising targets.

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Pathophysiology

- Platelet derived growth factor (PDGF) associated with PH and lung fibrosis.
- PDGF is found in several cell types including epithelial cells and SMCs.
- Acts via its 2 receptors PDGFα & PDGFβ, with an intracellular tyrosine kinase domain which can be inhibited by specific TKIs.
- PDGF activation promotes proliferation, migration and survival of SMCs in PAH.
- Targeting PDGF considered a target in PH .

Sc… tested,
no… Imatinib, Sorafenib ,linifanib and nintedanib

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Pulmonary Vascular Remodeling in PAH: A Cancer-Like Pattern?

- In a certain way, the cellular and biomolecular abnormalities expressed by pulmonary arteries in PAH share common features with neoplastic process.
- PAH and cancer share similarities in cellular pathological behavior insensitivity to antigrowth signals, evading apoptosis, limitless replicative potential, and change in cellular metabolism.
- Differences between the pathobiology of PAH and oncogenic processes are (lack of capability for tissue inva… sustained angiogenes…s).

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Indication of TKIs

- Chronic myeloid leukemia(CML),
- Gastrointestinal stromal tumor,
- HCC
- RCC

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Evidences of TKIs Value in PAH Treatment.

Imatinib (Gleevec, Novartis),

- A first case report of PAH treatment was published in 2005.
- A Pt with PAH in (NYHA) IV,
- Already in triple therapy with PAH-specific drugs,
- Was treated with imatinib 200 mg once daily.
- After 3 months of treatment, the patient's condition had improved markedly, with improvement of 6MWT distance, hemodynamic measurements, and functional class falling in class II.
- Improvement was sustained during a six-month follow-up with no evidence of side effects.

•(GhofraniHA,SeegerW,GrimmingerF.Imatinibforthetreatment of pulmonary arterial hypertension. N Engl J Med 2005;353 (13):1412–1413

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Evidences of TKIs Value in PAH Treatment

Imatinib (Gleevec, Novartis),

- **Soon after the description of this single case, 2 other cases of long-term treatment by imatinib in PAH patients were reported.**

- **They were stabilized or improved by using imatinib (alone or with bosentan) as a treatment of concomitant CML**

Souza R,SitbonO,ParentF,SimonneauG,HumbertM.Longterm imatinib treatment in pulmonary arterial hypertension. Thorax 2006;61(8):736)

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Clinical trials

Lung disease documented PDGF - PDGFR involved in pathogenesis	Drug	Completed cl study, st phase , st design & NO of pts	Patient population	Intervention	Primary outcome	Results
IPAH PDGF-BB PDGFR-β	Imatinib mesylats	IMPRES,Phase3, 24wks, multicentre, randomised, double blind, placebo controlled(n=202)	PVR□800dyns·cm−5 symptomatic on□2PAH therapies	Randomised to receive imatinib 200 mg once daily or placebo	Change in 6MWD	Mean treatment effect on 6MWD 32m;**p=0.002** PVR decreased by 379dyn·s·cm−5 **p<0.001** Serious AEs were more frequent with imatinib compared to placebo (44%versus30%)
	Sorafenib	GOMBERG-MAITLAND etal. Phase1b,16weeks , single center, open label(n=22)	Advanced but stable PAH on parenteral prostanoids (with or without oral sildenafil)	Received sorafenib started at 200mg daily then escalated to 400mg twice daily	Safety and tolerability	Sorafenib was well tolerated at 200mg twice daily AEs: moderate skin reactions on the hands and feet and alopecia

Clinical trials

- **IMPRES (Imatinib(in PAH, a Randomized Efficacy Study), a 24 wks phase III study, to evaluate imatinib in 202 severe PAH patients (PVR > 800 dyn/s/cm5) already treated with at least 2 PAH-specific drugs.**
- **The study met its I ry endpoint with a significant improvement in the 6MWT distance (+32 m in imatinib group vs. placebo , p=0.002).**
- **PVR was significantly decreased with a conclusive improvement in cardiac output.**
- **NT-pro-BNP was also significantly decreased in imatinib group.**
- **No improvement in NYHA functional class or delay in clinical worsening was observed.**
- **A treatment dose of 200 mg once daily, increased to 400 mg once daily after 2weeks if well tolerated.**

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Clinical trials

- **IMPRES study was followed by a 3-year open-label extension phase including 143 pts, all of them treated with Imatinib.**
- **Analysis of safety was reported with frequent but moderate adverse events in 112 pts:**
  - **Nausea 30.8%, --- vomiting18.2%, ----**
  - **Peripheral edema 16.8%, ----**
  - **ENT symptoms 15.4%, -----periorbital edema 15.4%,**
  - **headache 14.7%, and diarrhea 12.6%. ++++++**
  - **9 cases of subdural hematoma .**

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Clinical trials
Sorafenib

- Approved in advanced HCC, advanced clear-cell renal-cell carcinoma. and differentiated thyroid cancer)
- **In a 16 weeks phase Ib study, sorafenib has been evaluated in clinically stable PAH pts under parenteral prostanoids with NYHA from I to III.**
- **This single-center open label trial including 12 pts was designed to assess safety endpoints.**
- **The dose was 200 mg twice daily.**
- **Adverse events ,were moderate skin reactions, diarrhea,**

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Clinical trials
Sorafenib

- **Conclusion: -**

No clinical improvement was noticed.

During hemodynamic follow-up, cardiac output (CO) was significantly decreased, although still ranging in normal values without evidence of cardiac insufficiency symptoms with no significant difference in m PAP and PVR.

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Clinical trials

Nilotinib

- **Nilotinib is a 2nd -generation oral TKI approved for the treatment of CML in case of imatinib resistance or intolerance.**
- **Is currently under investigation in human PAH with a phase II clinical trial designed to establish safety and hemodynamic efficacy with decrease in pulmonary artery resistance as primary end point.**
- **Nilotinib has a more favorable safety profile than imatinib, although it is associated with a risk of cardiac co[illegible].**

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Vascular Side Effect of TKI

- New onset or worsening systemic HTN in >50% of Pts.
- Chest pain can occur in up to 15% of Pts, ranging from stable angina to ACS, even Takotsubo CM.
- Acute thromboembolic events 2-3%.

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Side Effect of TKI.

	HTN	Angina	AMI	Takotsubo	Ryanuads	stroke	PAD	Pul HTN	DVT/PE
sorafinib	X	X	X			X			X
Sunitinib	X	X	X	x		X			X
Pazobanib	X	X	X			X			X
Axitinb	X	x	X			X			X
Regorafinib	X	x	X						
Cabozanitib	X		X			X			X
Vandetinib	X					X			
Lenavitinb	x	X	X			X			X
Nilotinib		X	X			X			X
Ponatinib	x		x			x	x		x
Dasatinib							x	x	

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Side Effect of TKI.

CASE REPORT Open Access

Pulmonary arterial hypertension in a patient treated with dasatinib: a case report

Andris Skride[1,2], Matiss Sablinskis[3], Kristaps Sablinskis[3], Krista Lesina[1,2], Aivars Lejnieks[1,3] and Sandra Lejniece[1,3*]

Abstract

Background: There have been several reports on dasatinib-induced reversible pulmonary hypertension. This is the first reported case in Latvia; the patient did not discontinue the drug after the first adverse effects in the form of pleural effusions, which we speculate led only to partial reversion of the disease.

Case presentation: A 67-year-old white man with chronic myelogenous leukemia was treated with the dual Src and BCR-ABL tyrosine kinase inhibitor dasatinib. After treatment with dasatinib he had multiple pleural effusions which were suspected to be caused by congestive heart failure. Later a transthoracic Doppler echocardiography and right-sided heart catheterization revealed severe pulmonary hypertension with pulmonary vascular resistance of 12 Wood units and mean pulmonary artery pressure of 53 mmHg. Computed tomography ruled out a possible pulmonary embolism; laboratory specific tests for human immunodeficiency virus, rheumatoid factor, and anti-nuclear antibodies were negative, and dasatinib-induced pulmonary arterial hypertension was diagnosed.
A follow-up right-sided heart catheterization and 6-minute walk test done a month after the discontinuation of dasatinib showed significant improvement: mean pulmonary artery pressure of 34 mmHg and pulmonary vascular resistance of 4 Wood units.

Conclusions: Patients should always be closely monitored when using dasatinib for a prolonged time. Dasatinib-induced pulmonary hypertension may be fully reversible after the therapy is suspended, but the key factors involved are still unclear and need to be further studied.

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- A 67-year-old man with chronic myelogenous leukemia.
- Was treated with tyrosine kinase inhibitor (dasatinib).
- After treatment he had multiple pleural effusions ,suspected to be caused by CHF.
- Echo & RT heart cath revealed severe PH with PVR of 12 Wood units and mean PAP of 53 mmHg.
- CT ruled out a possible PE.
- LAP test for HIV, rheumatoid F, and ANA were negative.
- Dasatinib-induced PAH was diagnosed.
- A follow-up RT heart cath and 6-MWT done a month after the discontinuation of dasatinib showed significant improvement:
- Mean PAP of 34 mmHg and PVR of 4 Wood units.

Skride et al. Journal of Medical Case Reports (2017) 11:362
DOI 10.1186/s13256-017-1515-9

Journal of Medical Case Reports

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Conclusions: Patients should always be closely monitored when using dasatinib for a prolonged time. Dasatinib-induced pulmonary hypertension may be fully reversible after the therapy is suspended, but the key factors involved are still unclear and need to be further studied.

Keywords: Pulmonary arterial hypertension, Dasatinib, Chronic myelogenous leukemia, Pleural effusion

- Another case report of dasatinib induced PH did not improved by discontinuation of dasatinib

International Journal of Medical and Pharmaceutical Case Reports

9(3): 1-4, 2017; Article no.IJMPCR.34110
ISSN: 2394-109X, NLM ID: 101648033

Tyrosine Kinase Inhibitor Induced Pulmonary Artery Hypertension: Reversible with Ponatinib?

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJMPCR/2017/34110
Editor(s):
(1) Syed A. A. Rizvi, Department of Pharmaceutical Sciences, College of Pharmacy, Nova Southeastern University, USA.
Reviewers:
(1) Ramachandran Muthiah, Thoothukudi Medical College Hospital, Thoothukudi, India.
(2) Arthur Nwafor Chuemere, University of Port Harcourt, Nigeria.
(3) L. I. Audu , National Hospital Abuja, University of Abuja, Nigeria.
Complete Peer review History: http://www.sciencedomain.org/review-history/19497

Case Study

Received 14th May 2017
Accepted 8th June 2017
Published 12th June 2017

ABSTRACT

Pulmonary arterial hypertension (PAH) is a disease associated with progressive and comprehensive vascular remodeling of small pulmonary arteries. The prognosis of Chronic myelogenous leukemia (CML) has been improved by tyrosine kinase inhibitors (TKIs), which inhibit BCR/ABL kinase pathway. Most of the TKIs induced PAH is limited almost exclusively to dasatinib until now. There was only one report about, PAH was caused by the novel TKI ponatinib. We present a 73 years old-female patient with chronic myeloid leukemia, who had PAH after approximately 72 months with prior exposure to dasatinib. Dasatinib was replaced by nilotinib in this patient. Nilotinib was used 11 months for CML treatment, but no recovery was seen with also this TKI. Finally, ponatinib therapy was started for CML. Signs and symptoms of PAH improved with institution of ponatinib therapy. Therefore we report that the patient with dasatinib induced PAH did not recover after institution of nilotinib as a TKI instead of dasatinib but improved with ponatinib treatment using for CML.

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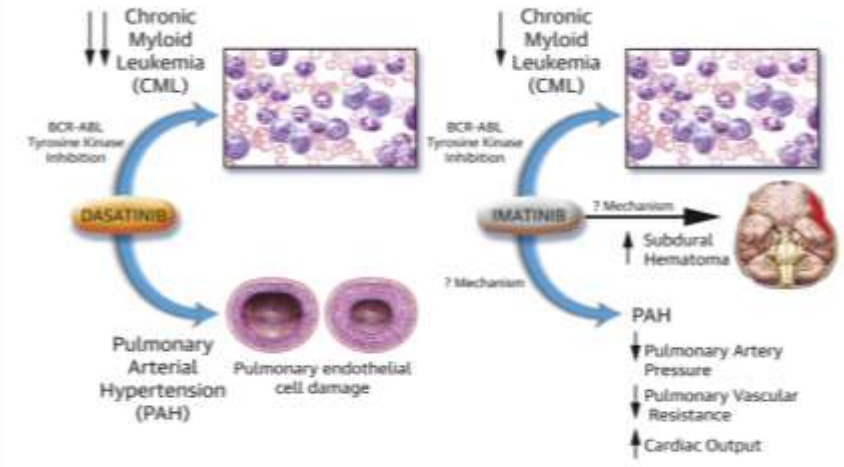
CENTRAL ILLUSTRATION **Contrasting Effects of Dasatinib and Imatinib on the Pulmonary Vasculature**



Ryan, J.J. J Am Coll Cardiol Basic Trans Science. 2016;1(7):684-6.

CML = chronic myeloid leukemia; PAH = pulmonary arterial hypertension.

- In trial to decrease SE of TKI .
- Inhalation TKIs were evaluated in one study.

Inhaled tyrosine kinase inhibitors for pulmonary hypertension: a possible future treatment

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
7 October 2014
Number of times this article has been viewed

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Abstract: Pulmonary hypertension is a disease with severe consequences for the human body. There are several diseases and situations that induce pulmonary hypertension and are usually underdiagnosed. Treatments include conventional medical therapies and oral, inhaled, intravenous, and subcutaneous options. Depending on its severity, heart or lung transplant may also be an option. A possible novel treatment could be tyrosine kinase inhibitors. We conducted experiments with three jet nebulizers and three ultrasound nebulizers with erlotinib, gefitinib, and imatinib. Different residual cup designs and residual cup loadings were used in order to identify the best combination to produce droplets of less than 5 μm in mass median aerodynamic diameter. We found that gefitinib could not be transformed into a powder, so conversion to an aerosol form was not possible. Our experiments indicated that imatinib is superior to erlotinib with regard to small droplet size formation using both inhaled technologies (1.37 μm <2.23 μm and 1.92 μm <3.11 μm, jet and ultrasound, respectively) and, at jet devices (1.37 μm <1.92 μm). Cup designs C and G contribute best to small droplet creation uniquely supporting and equally well the activity of both drugs. The disadvantage of the large droplets formed for erlotinib was offset when combined with residual cup C (1.37 μm instead of 2.23 μm). At a 2 mL dose, the facemask and cone mouthpieces performed best and evenly; the facemask and low dose were the best choice (2.08 μm and 2.12 μm, respectively). Erlotinib and imatinib can be administered as an aerosols, and further in vivo experimentation is necessary to investigate the positive effects of these drugs in the treatment of pulmonary hypertension.

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Conclusion of this study

- TKIs already on the market can be modified to be produced as aerosols that could be used as a treatments for PH. Specifically, imatinib known to cause severe dose- dependent SE when administered systemically
- Currently one TKI is under development for inhalation by Pfizer and is being investigated in a Phase I.

Conclusions

- **TKIs have revolutionized the Felid of cancer therapy and are prescribed so commonly nowadays that cardiologists should be familiar with their cardiovascular side effects.**
- **The future of PAH therapy relies on unlocking the secret of the hyperproliferative pathway in PAH**
- **TKIs represent a new and hopeful treatment in PAH.**
- large inhibition spectrum and lack of specificity of TKI suspect the emergences of unexpected toxicities, including pulmonary vascular harmfulness.
- TKIs currently available seem to have a poor benefit/risk ratio in the context of PAH

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Conclusions

- **A future clinical trial is needed to determine the effectiveness of aerosolized TKIs for PH**

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Thank you

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