Why does ibrutinib carry a risk of cerebral aspergillosis?

Georgios Chamilos, MD
School of Medicine, University of Crete
hamilos@imbb.forth.gr
I have no idea!!!

- I asked two experts scientists working on BTK signaling and Aspergillus
  - Michalis Lionakis (Cancer Cell, 2017 Jun 12;31(6):833-843.e5)
- The also had no clue!
- I will try to address the following questions:
  1. Is ibrutinib associated with increased risk for invasive aspergillosis?
  2. Is ibrutinib associated with increased risk for cerebral aspergillosis?
  3. Which are the mechanisms of ibrutinib-associated immunosuppression?
- I will have to make assumptions based on the published literature
- If anyone in the room knows the answer please let me know!
Ibrutinib: a “game-changing drug” in B-cell malignancies (accelerated FDA Approval in 2013)

Byrd et al., J Clin Oncol, 2014, 32:3039-3048


4 year follow up: only 12% of patients D/C due to AEs (AF, bleeding, infection)
X-Linked Agammaglobulinemia

Report on a United States Registry of 201 Patients

Jerry A. Winkelstein, MD, Mary C. Marino, MLS, Howard M. Lederman, MD, PhD, Stacie M. Jones, MD, Kathleen Sullivan, MD, PhD, A. Wesley Burks, MD, Mary Ellen Conley, MD, Charlotte Cunningham-Rundles, MD, PhD, and Hans D. Ochs, MD

Diagnostic Criteria

- Positive Family History
- Mutation in BTK
- Absent B cells and Hypogammaglobulinemia

Winkelstein JA et al., Medicine, 2006; 85:195-202

<table>
<thead>
<tr>
<th>Infection</th>
<th>No. of Patients (%)</th>
<th>(n = 201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory</td>
<td></td>
<td>140 (70)</td>
</tr>
<tr>
<td>Otitis</td>
<td></td>
<td>119 (59)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td></td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Mastoiditis</td>
<td></td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td>125 (62)</td>
</tr>
<tr>
<td>Chronic/recurrent diarrhea</td>
<td></td>
<td>46 (23)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td></td>
<td>42 (21)</td>
</tr>
<tr>
<td>Pyodermia/cellulitis/subcutaneous abscess</td>
<td></td>
<td>36 (18)</td>
</tr>
<tr>
<td>7Meningitis/encephalitis</td>
<td></td>
<td>25 (12)</td>
</tr>
<tr>
<td>Sepsis</td>
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<td>21 (10)</td>
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</table>

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of Patients (%)</th>
<th>(n = 125)</th>
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<tbody>
<tr>
<td>Pneumococcus</td>
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<td>9 (7)</td>
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<tr>
<td>H. influenzae, type b</td>
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<td>5 (4)</td>
</tr>
<tr>
<td>Pseudomonas spp</td>
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<td>3 (2)</td>
</tr>
<tr>
<td>Staphylococcus spp</td>
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<td>3 (2)</td>
</tr>
<tr>
<td>H. parainfluenza</td>
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<td>3 (2)</td>
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<tr>
<td>H. parahemolytica</td>
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<tr>
<td>Klebsiella spp</td>
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<td>1 (1)</td>
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<tr>
<td>Mycobacterium avium</td>
<td></td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pneumocystis carinii</td>
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<td>1 (1)</td>
</tr>
<tr>
<td>Measles</td>
<td></td>
<td>1 (1)</td>
</tr>
<tr>
<td>Unknown/not reported</td>
<td></td>
<td>105 (84)</td>
</tr>
</tbody>
</table>

OIs
Atypical *Pneumocystis jirovecii* pneumonia in previously untreated patients with CLL on single-agent ibrutinib

Inhye E. Ahn,1,* Theresa Jerussi,2,* Mohammed Farooqui,3 Xin Tian,4 Adrian Wiestner,3 and Juan Gea-Banacloche5

Open Forum Infectious Diseases

**BRIEF REPORT**

Disseminated Cryptococcosis With Brain Involvement in Patients With Chronic Lymphoid Malignancies on Ibrutinib

Ibrutinib for Chronic Lymphocytic Leukemia

*NEJM* 374:16 NEJM.ORG APRIL 21, 2016

**TO THE EDITOR:** Burger et al. report promising results of ibrutinib as initial therapy for CLL. After a median follow-up of 18.4 months, three deaths occurred in the ibrutinib group, one from klebsiella infection and two from unknown causes.

We report on brain abscesses due to aspergillosis, a rare occurrence in CLL, which developed during ibrutinib therapy. Invasive aspergillosis developed in three patients with relapsed CLL within 2 months after the initiation of ibrutinib.

Inhibition of B Cell Receptor Signaling by Ibrutinib in Primary CNS Lymphoma

94% showed tumor reductions with ibrutinib alone, including patients having PCNSL with *CD79B* and/or *MYD88* mutations, and 36% of evaluable patients achieved complete remission with DA-TEDDi-R. *Increased aspergillosis was observed with ibrutinib monotherapy and DA-TEDDi-R. Aspergillosis was linked to BTK-dependent fungal immunity in a murine model. PCNSL is highly dependent on BCR signaling, and ibrutinib appears to enhance the efficacy of chemotherapy.*

Lionakis et al., 2017, Cancer Cell 31, 833–843
Relatively low frequency of Invasive Aspergillosis (IA) in other clinical studies on ibrutinib

<table>
<thead>
<tr>
<th>Type and Status of Cancer</th>
<th>Type of IFI (No. of Cases)</th>
<th>Frequency of IFI, %</th>
<th>Patients, No.</th>
<th>Median follow-up, mo</th>
<th>Study timing, month/Year</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsed CLL</td>
<td>Cryptococcosis (1)</td>
<td>1.2</td>
<td>85</td>
<td>20.9</td>
<td>5/2010-2/2013</td>
<td>Byrd et al</td>
</tr>
<tr>
<td>Relapsed CLL/SLL</td>
<td>IA (2)</td>
<td>0.5</td>
<td>391</td>
<td>9.4</td>
<td>6/2012-11/2013</td>
<td>Byrd et al</td>
</tr>
<tr>
<td>Relapsed WM</td>
<td>IA (1)</td>
<td>3.2</td>
<td>31</td>
<td>18.1</td>
<td>8/2014-2/2015</td>
<td>Dimopoulos et al.</td>
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<tr>
<td>Relapsed MCL</td>
<td>Cryptococcosis (1), PJP (1), histoplasmosis (1)</td>
<td>2.7</td>
<td>111</td>
<td>26.7</td>
<td>2/2011-1/2014</td>
<td>Wang et al.</td>
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<tr>
<td>CLL</td>
<td>1 IA, 1 fungal pneumonia</td>
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<td>127</td>
<td>13</td>
<td>7/2010-5/2014</td>
<td>Jain et al.</td>
</tr>
<tr>
<td>Relapsed/refractory DLBCL</td>
<td>None</td>
<td>0</td>
<td>80</td>
<td>11.5</td>
<td>5/2012-5/2013</td>
<td>Wilson et al.</td>
</tr>
<tr>
<td>Refractory CLL/SLL</td>
<td>PJP (1)</td>
<td>0.7</td>
<td>145</td>
<td>27.6</td>
<td>1/2013-6/2013</td>
<td>O’Brien et al.</td>
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<tr>
<td>Refractory PCNSL</td>
<td>IA (7), PJP (1)</td>
<td>44</td>
<td>18</td>
<td>15.5</td>
<td>8/2014-3/2016</td>
<td>Lionakis et al.</td>
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<td>Refractory PCNSL</td>
<td>IA (2)</td>
<td>11</td>
<td>18</td>
<td>N/A</td>
<td>9/2015-8/2016</td>
<td>Choquet et al</td>
</tr>
<tr>
<td>Refractory PCNSL</td>
<td>IA (1)</td>
<td>5</td>
<td>20</td>
<td>N/A</td>
<td>N/A</td>
<td>Grommes et al.</td>
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Ibrutinib related infections in clinical practice

- **Real Word Toxicity**: up to 42% of 621 relapsed patients D/C ibrutinib due to AEs at a median time of 6 months (*Mato AR, Ann Oncol 2017, 28:1050-1056*)

- Phase Ib trial in relapsed refractory CLL patients
  - Grade 3+ infection in 51% of patients (25% pneumonia grade 3+), *Byrd JC, N Engl J Med, 2013 Sep 26;369(13):1278-9*

- In 148 malignancy patients (95% CLL), **8.1% OIs** among 148 hematological malignancy patients receiving first-line BTK inhibitors (*Issa N et al., Open Forum Infect Dis 2017l 4 (suppl 1):S699*)
Is ibrutinib therapy associated with increased risk for development of Invasive Aspergillosis?

Increased susceptibility of mice for IA upon pharmacological or genetic ablation of BTK

Stadler N et al., Haematologica 2017 102:e191-194

Lionakis MS et al., Cancer Cell 2017 31, 833-843
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<td>No</td>
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<td>Arthus et al.</td>
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<td>CNS, lungs</td>
<td>2 wks</td>
<td>76/F</td>
<td>PCNSL</td>
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<td>Dead</td>
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<tr>
<td>CNS, lungs</td>
<td>3 months</td>
<td>87/F</td>
<td>PCNSL</td>
<td>Active</td>
<td>Yes</td>
<td>Dead</td>
<td>Lionakis et al.</td>
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<tr>
<td>Lungs</td>
<td>4 months</td>
<td>60/M</td>
<td>PCNSL</td>
<td>Active</td>
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<td>Alive</td>
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<td>Lungs</td>
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<td>N/A</td>
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<td>Kreiniz et al.</td>
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Is ibrutinib associated with increased risk for cerebral aspergillosis?

CNS aspergillosis in 9/14 (64%)
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IA within the first 4 months (> 93%)
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45% of cases of CNS aspergillosis in pts with brain pathology
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<td>Lionakis et al.</td>
</tr>
<tr>
<td>CNS, lungs</td>
<td>2 wks</td>
<td>65/M</td>
<td>PCNSL</td>
<td>Active</td>
<td>Yes</td>
<td>Dead</td>
<td>Lionakis et al.</td>
</tr>
<tr>
<td>CNS, lungs</td>
<td>3 months</td>
<td>87/F</td>
<td>PCNSL</td>
<td>Active</td>
<td>Yes</td>
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</tr>
<tr>
<td>Lungs</td>
<td>4 months</td>
<td>60/M</td>
<td>PCNSL</td>
<td>Active</td>
<td>Yes</td>
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<tr>
<td>Lungs</td>
<td>2 months</td>
<td>53/M</td>
<td>PCNSL</td>
<td>Active</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Lungs</td>
<td>1 month</td>
<td>64/M</td>
<td>PCNSL</td>
<td>Active</td>
<td>Yes</td>
<td>Alive</td>
<td>Lionakis et al.</td>
</tr>
<tr>
<td>CNS, lungs</td>
<td>2 wks</td>
<td>49/M</td>
<td>PCNSL</td>
<td>Active</td>
<td>Yes</td>
<td>Alive</td>
<td>Lionakis et al.</td>
</tr>
<tr>
<td>Sinusitis, CNS</td>
<td>3 wks</td>
<td>75/F</td>
<td>CLL</td>
<td>PD</td>
<td>No</td>
<td>Alive</td>
<td>Baron et al.</td>
</tr>
<tr>
<td>CNS, lungs</td>
<td>2 months</td>
<td>76/NA</td>
<td>CLL</td>
<td>PD</td>
<td>No</td>
<td>Dead</td>
<td>Jain et al.</td>
</tr>
<tr>
<td>Lungs</td>
<td>7 months</td>
<td>67/M</td>
<td>CLL</td>
<td>N/A</td>
<td>No</td>
<td>Dead</td>
<td>Kreiniz et al.</td>
</tr>
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Refractory of relapsed malignancy in 100% of patients
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<thead>
<tr>
<th>Type of IA</th>
<th>Time after treatment</th>
<th>Age/Sex</th>
<th>Type of Cancer</th>
<th>Status of Malignancy</th>
<th>Concomitant steroids</th>
<th>Outcome</th>
<th>Ref</th>
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<tbody>
<tr>
<td>CNS</td>
<td>1 month</td>
<td>N/A</td>
<td>CLL</td>
<td>PD</td>
<td>Yes</td>
<td>Dead</td>
<td>Ruchlemer et al.</td>
</tr>
<tr>
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<td>2 months</td>
<td>N/A</td>
<td>CLL</td>
<td>PD</td>
<td>Yes</td>
<td>Alive</td>
<td>Ruchlemer et al.</td>
</tr>
<tr>
<td>CNS</td>
<td>2 months</td>
<td>N/A</td>
<td>CLL</td>
<td>PD</td>
<td>Yes</td>
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<td>Ruchlemer et al.</td>
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<tr>
<td>Lungs</td>
<td>6 wks</td>
<td>62/M</td>
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<td>PD</td>
<td>No</td>
<td>Alive</td>
<td>Arthus et al.</td>
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<tr>
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<td>2 wks</td>
<td>76/F</td>
<td>PCNSL</td>
<td>Active</td>
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<td>Dead</td>
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<td>No</td>
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<td>Kreiniz et al.</td>
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</table>

71% of patients also received corticosteroids
• Retrospective surveillance (French Innovative Leukemia Organization for CLL)

• 33 cases of IFI from 16 Cancer Centers from 2013-2017

• Invasive aspergillosis in 27/33 (81%) within 3 months of ibrutinib treatment

• CNS aspergillosis in 11/27 (40%)

• All refractory/relapsed disease

• Additional predisposing factors in most of patients (steroids in 7, neutropenia in 5)
Conclusions

- Ibrutinib treatment increases the risk for development of IA
- CNS dissemination is a frequent event in ibrutinib-related aspergillosis
- Ibrutinib-associated IA occurs in the setting of additional immunosuppressive conditions:
  - Corticosteroids
  - Refractory/relapsed hematological malignancy
  - Brain pathology due to the underling disease (microglia?)
- Environmental exposures and other epidemiological factors could be also implicated in ibrutinib-associated aspergillosis
Lessons from primary immunodeficiencies predisposing to Aspergillus

- Functional defects in myeloid cells
  - Job’s syndrome (STAT3)
  - CGD (NADPH oxidase)
    - Pulmonary alveolar proteinosis (GM-CSF signaling)
- Defects in myeloid cell numbers (including chemotaxis)
  - MonoMAC syndrome (GATA2)-numbers
  - Severe congenital neutropenia (ELA2, HAX1)-numbers
  - Leucocyte adhesion deficiency (CD18)-trafficking
- **CARD9 deficiency (ONLY IMMUNODEFICIENCY LINKED TO CEREBRAL ASPERGILLOSIS)-defect in neutrophil chemotaxis** (Rieber N et al., JCI Insight. 2016 Oct 20;1(17):e89890)
Unique predisposing factors for CNS aspergillosis

- Case series (14 cases, MGH: 2000-2011) and literature review
- Lung was the primary focus (11/14)
- Predisposing factors
  - Corticosteroids (10/14, 71%)
  - Neutropenia (6/14, 43%)
  - Metabolic diseases
    - Diabetes mellitus in 3 (21%), hepatic insufficiency in 3 (21%)
- Previous brain pathology in 8/14 (57%)

Kourkoumpetis TK et al., Medicine 2012;91: 328Y336
Literature review of 123 additional cases of CNS aspergillosis

- Literature review of 123 cases
- 60 (49%) patients on immunosuppressive therapy
  - **C/steroids (22%)**, CsA (4.1%), Tacrolimus (1%), anti-TNF (1%)
- No underlying disease in 23/123 (24%)
- Diabetes mellitus in 18% of patients (paranasal involvement)
- 5% of patients had **previous brain pathology**
- *A. fumigatus* (33.3%), *A. flavus* (6%)

Kourkoumpetis TK et al., Medicine 2012;91: 328Y336
Potential mechanisms of ibrutinib-related IA

- Defect(s) in myeloid cell function(s)?
Defects in BTK expression in monocytes of XLA patients

![Image of Western blot analysis showing normal and partial BTK expression in different cell types.](image)

- **Normal BTK expression**
- **Partial BTK deficiency**

Frequency:
- Patient: 30/41
- Mother: 5/41

BTK deficiency results in broad immune defects in myeloid cells: PMNs

CNS Inflammation

PMN phagocytosis, chemotaxis and differentiation


BTK deficiency results in broad immune defects in myeloid cells: Macrophages

TNF production in Macrophages

Inflammasome activation in Macrophages

Ito M et al., Nat Commun. 2015 Jun 10;6:7360
BTK deficiency results in broad immune defects in myeloid cells: Microglia

VaV/BTK dependent phagocytosis

Strijbis K et al., PLoS Pathog 2013

VaV dependent ROS production

Shah VB et al., Molecular Immunology 46 (2009) 1845–1853
BTK/Calcineurin signaling activation during Aspergillus infection in macrophages

Physiological Immune Response against Aspergillus

Resident myeloid cells (AMs, DCs) → IL1R/MyD88 → PTX3 → PMNs → Ly6C^hi^ monocytes

CARD9 signaling → Type I, III IFNs

Killing by AMs/monocytes → Noncanonical autophagy-dependent killing

NETosis → ROS-dependent killing via apoptosis

Antimicrobial peptides
Nutritional Immunity (Zn2+, lactotransferin)

Jhungar A et al., PLoS Pathog 2015 11:e1004589
Espinosa V et al., PLoS Pathog 10:e1003940
Hohl T et al., Cell Host Microbe 2009 6:470-81
Hohl TM PLoS Pathog 2005 1 e30
Caffrey AK, PLoS Pathog 2015 11:e1004625
Zelante T et al. Mucosal Immunol 2017 10:470-480
Rieber N et al., JCI Insight. 2016 Oct 20;1(17):e89890
Akoiananaki et al., Cell Host Microbe 2016; 19:79-90
Shah A et al., Am J Respir Crit Care Med. 2016 Nov 1;194(9):1127-1139
Herbst S et al., EMBO Mol Med. 2015 Mar;7(3):240-58
Potential immune defects caused by inhibition of BTK

Resident myeloid cells (AMs, DCs)

Alveolar epithelia

CARD9 signaling

PMNs

Ly6C\textsuperscript{hi} monocytes

Type I, III IFNs

↑ ROS

ROS dependent-killing via apoptosis

Antimicrobial peptides

Nutritional Immunity (Zn\textsuperscript{2+}, lactotransferin)

Killing by AMs/monocytes

Noncanonical autophagy-dependent killing

Netosis

ROS dependent-killing

Herbst S et al., EMBO Mol Med. 2015 Mar;7(3):240-58

Shah A et al., Am J Respir Crit Care Med. 2016 Nov 1;194(9):1127-1139

Zelante T et al. Mucosal Immunol 2017 10:470-480
Additive immunosuppressive action of corticosteroids on BTK inhibition?
Killing of *Aspergillus* inside macrophages

- Resting spores
- Phagocytosis
- Cell wall swelling
- ROS
- Killing
- Host immune response
- Corticosteroids
- GCD
- Lys

Philippe B and Latge JP., I&I 2003; 71:891-903
Corticosteroid-induced immunosuppression is characterized by broad defects in phagosome biogenesis

Lysosomal Stability during Phagocytosis of Aspergillus flavus Spores by Alveolar Macrophages of Cortisone-Treated Mice

LC3 associated phagocytosis (LAP) regulates *Aspergillus* killing by phagocytes

Kyrmizi et al. J Immunol 2013
Aspergillus melanin targets LAP to promote pathogenicity

Akoumianaki T et al., Cell Host Microbe, 2016
Signaling pathways regulating immunity against *Aspergillus* inside macrophages

A specialized Ca2+ signaling pathway regulates LAP

Kyrmizi et al., (under review)
Kyrmizi et al., (under review)
A specialized Ca2+/Calmodulin (CaM) signaling regulates LAP

Kyrmizi et al., (under review)
Calcineurin inhibitors do not inhibit *Aspergillus* LAP

Calcineurin inhibitors do not inhibit *Aspergillus* LAP. The graphs show the concentration of TNF (pg/mL) and the percentage of LC3+ phagosomes with and without CsA (ng/ml) treatment. The images display fluorescent microscopy of LC3, FITC conidia, and merge for WT and ΔpksP strains under different treatments. The CFUs are counted for each condition.

**Graphs:**
- TNF (pg/mL) vs. CsA (ng/ml) for WT and ΔpksP.
- % LC3+ phagosomes vs. CsA (ng/ml) for WT and ΔpksP.

**Images:**
- Fluorescent microscopy images of WT and ΔpksP strains under different CsA treatments.
- CFUs for WT and ΔpksP strains at 24h (MOI 1:10) with or without CsA (1000 ng/ml).

**Legend:**
- **WT**: Wild type
- **ΔpksP**: ΔpksP mutant
- **CsA**: Calcineurin inhibitor
- **NS**: Not significant
Additive immunosuppressive action of corticosteroids on BTK inhibition

Resident myeloid cells (AMs, DCs)

Herbst S et al., EMBO Mol Med. 2015 Mar;7(3):240-58

Killing by AMs/monocytes

Lionakis MS et al., Cancer Cell 2017 31, 833-843

Carboxen

C/steroids

Noncanonical autophagy-dependent killing

ROS dependent-killing

NETosis

Shah A et al., Am J Respir Crit Care Med. 2016 Nov 1;194(9):1127-1139

Lateral transfer (Metaphorosis)

CARD9 signaling

Zelante T et al. Mucosal Immunol 2017 10:470-480

IL1R/MyD88

PTX3

PMNs

Ly6Chi monocytes

TNF, chemokines

Type I, III IFNs

↑ ROS

ROS dependent-killing via apoptosis

Antimicrobial peptides

Nutritional Immunity
(Zn2+, lactotransferin)
CNS dissemination of *Cryptococcus*: a Trojan horse hypothesis
A “Trojan horse” hypothesis on *Aspergillus* persistence and CNS dissemination?

1. Phagosome maturation arrest
2. BTK-induced defects in phagocytosis, chemotaxis, effector function
3. Abnormalities in Nutritional Immunity

**Intracellular killing**

**Intracellular persistence**

**Dissemination (Trojan horse theory)?**
Additional risk factors in cases of ibrutinib-associated CNS aspergillosis?

- Immunodeficiency related to status and type of underlying malignancy
- Patient specific environmental exposures
- Off target effects?
- Genetic predisposition to IA
- Immune defects related to previous sepsis episodes
- Immunosuppressive effects of other drugs
- Pharmacogenomic and drug-drug interactions
- Uncharacterized pathogen-associated risk factors
Other SMKIs are associated invasive aspergillosis: the sorafenib story

*Bazaz R & DW Denning, Clin Infect Dis 2018 Jan 23

<table>
<thead>
<tr>
<th>Type of IFI</th>
<th>Sites of infection</th>
<th>Type of cancer</th>
<th>Age/Sex</th>
<th>Concomitant corticosteroids</th>
<th>Comorbidities</th>
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<tbody>
<tr>
<td>Subacute invasive aspergillosis*</td>
<td>lung</td>
<td>Hepatocellular carcinoma</td>
<td>64/M</td>
<td>No</td>
<td>DM, Asthma</td>
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Other SMKIs are associated invasive aspergillosis: the sorafenib story

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<td>Invasive aspergillosis</td>
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<td>Talaromyces marneffei infection</td>
<td>disseminated</td>
<td>AML</td>
<td>67/M</td>
<td>No</td>
<td>N/A</td>
</tr>
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</table>

*Bazaz R & DW Denning, Clin Infect Dis 2018 Jan 23
Chamilos G, Lionakis MS, Kontoyiannis DP, Clin Infect Dis 2018
Can we make predictions on the risk of treatment with certain SMKIs for IA?

Aspergillus fumigatus Induces Innate Immune Responses in Alveolar Macrophages through the MAPK Pathway Independently of TLR2 and TLR4

Marc Dubourdeau,* Rafika Athman,† Viviane Balloy,‡ Michel Huerre,§ Michel Chignard,‡ Dana J. Philpott,† Jean-Paul Latgé,* and Oumaïma Ibrahim-Granet2*  

CARD9 mediates Dectin-1–induced ERK activation by linking Ras-GRF1 to H-Ras for antifungal immunity

Xin-Ming Jia,1 Bing Tang,2 Le-Le Zhu,1 Yan-Hui Liu,1 Xue-Qiang Zhao,3 Sara Gorjestani,3 Yen-Michael S. Hsu,3 Long Yang,1 Jian-Hong Guan,1 Guo-Tong Xu,1 and Xin Lin3
The future of IMIs in the era of targeted therapies for malignant and autoimmune diseases?

• A surge of therapies with SMKIs targeting antifungal immune signaling pathways
  • BTK inhibitors
  • PI3K inhibitors
  • Syk inhibitors
  • NOX inhibitors
  • MAPK inhibitors
  • JAK/STAT inhibitors

• Additional IA cases associated with biological therapies
  • TNF inhibitors
  • eculizumab

Which should be the top priorities in research of IA associated with small molecule kinase inhibitors (SMKIs)?

- Better epidemiology tools and increased surveillance to capture Missed Aspergillosis Cases
- Mandatory report of IMIs in Clinical Trials
- Better risk stratification tools in low-risk patients
- Urgent need for development of novel biomarkers of immunodeficiency
- Preclinical studies on the risk of SMKIs for development of IMIs
- Basic research on IMI immunology and pathogenesis
- Basic research on understanding molecular mechanisms of immunodeficiency
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Lionakis MS, MD
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