Efficacy of Biologic Agents in the Treatment of Erdheim-Chester Disease

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Background – Interleukins in ECD

- Th1 mediated systemic immune response activation
- Increased serum levels of
  - IL-6,
  - IL-12,
  - Interferon-alfa (IFN-α), and
  - Monocyte chemotactic protein-1 (MCP-1)

Arnaud et al: Blood 117(10):2783, 2011

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Background

Reports of treatment with biologic agents:

- Interlukin-1 receptor (IL-1) antagonists (anakinra) in ECD
- Anti-tumor necrosis factor-alpha (TNF-α) inhibitors
  - Infliximab in ECD
  - Etanercept in LCH

Aouba et al: Blood 116(20):4070, 2010
Cohen-Aubert et al: Blood 127(11):1509, 2016
Dagna et al: J Clin Oncol 30(28):e286, 2012
Diamond et al: Blood 128(14):1896, 2016
Henter et al: N Engl J Med 345(21):1577, 2001
Killu et al: Int J Cardiol 167(5):e115, 2013

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Patients and Methods

- ECD patients evaluated at Mayo Clinic from January 1998 to August 2016 who received biologic agents in any line of therapy
- Diagnosis of ECD made by using clinical criteria in conjunction with histopathologic findings

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Methods

- Response criteria
  - No uniform post-therapy assessment performed
  - Two response criteria

Clinical response criteria	
Complete response (CR)	Complete resolution of symptoms attributed to ECD
Partial response (PR)	Incomplete resolution of symptoms for at least 3 months
Stable disease (SD)	No change in symptoms for at least 3 months
Progressive disease (PD)	Worsening of symptoms
Radiological response criteria	
Complete response (CR)	Complete resolution of proven or suspected lesion due to ECD
Partial response (PR)	Incomplete resolution of proven or suspected lesion due to ECD
Stable disease (SD)	No significant change in proven or suspected lesion due to ECD
Progressive disease (PD)	Progression/worsening of proven or suspected lesion due to ECD

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Results

Total ECD patients (1998-2016)	63
Median age	54 years (range, 34-80)
Site of ECD involvement	
Bone	91%
Kidney/retroperitoneum	67%
Central nervous system	42%
Patients treated with biologic agents	12 (19%)
Anakinra	8
Infliximab	5
Etanercept	2
Median duration of therapy (months)	12 (range, 1-133)
BRAF-V600E mutational testing	
Tested	9
Positive	8 (89%)

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Results

Clinical responses	Anakinra*	Infliximab**	Etanercept**
CR	1	0	0
PR	3	0	0
SD	0	1	0
PD	3	4	2
Radiological responses		0	0
CR	0	0	0
PR	2	0	0
SD	3	1	0
PD	2	3	1

* Median duration of response 42.5 months (range, 29-133)
* 1 patient had an ongoing response after 33 months of therapy
* 1 patient not evaluable (lost to follow up)
** 1 patient not evaluable radiologically

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Key Points: Anakinra

- Clinical responses:
  - Bone pain (n= 2),
  - Dyspnea (n= 2)
- Radiological responses:
  - Reduction in size of a right atrial mass (n=1),
  - Retroperitoneal fibrosis (n=1)
- Radiological progression:
  - Increase in size of a cerebellar ECD lesion (n=1)

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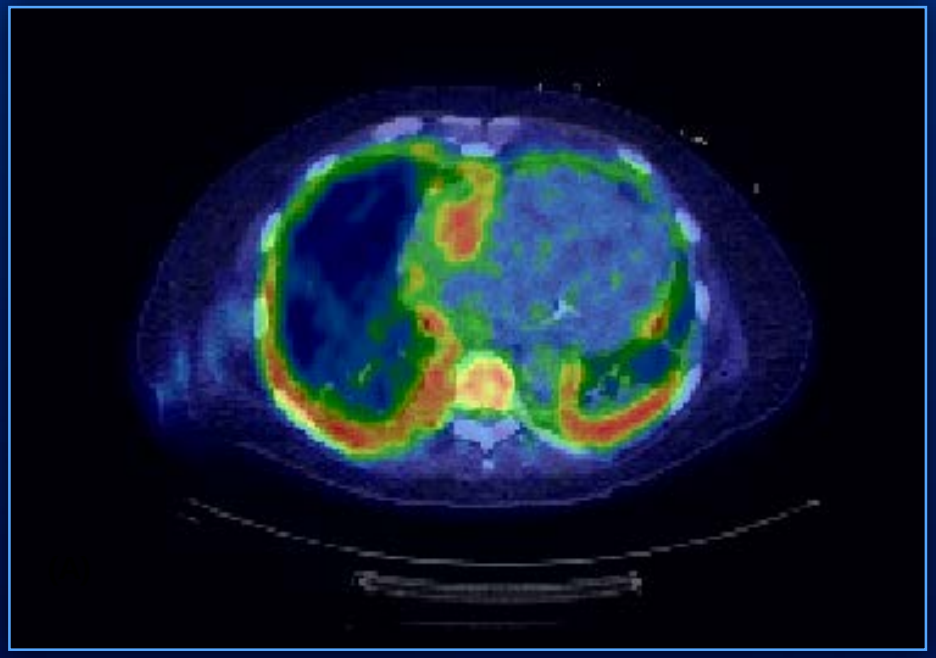
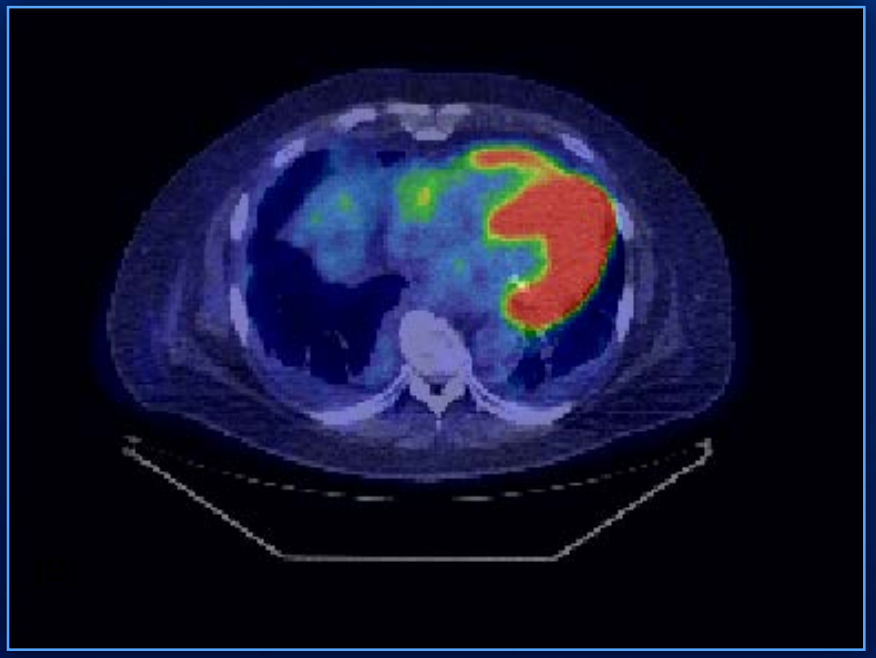
Before treatment



After treatment



- Decrease in activity of right atrial ECD lesion 2 months after therapy with anakinra
- There was additional infectious/inflammatory activity in the pleura bilaterally that resolved as well

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Key Points: Infliximab and Etanercept

- No clinical or radiological responses
- One patient noted stability of dizziness for 25 months on infliximab
- Two patients with worsening bone pain after etanercept

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Treatment-related Adverse Effects (CTCAE)

Anakinra [3/8 (38%) patients]

- Grade 2 thrombocytopenia (n=1)
- Grade 1 liver enzyme elevations (n=2)

Infliximab [2/5 (40%) patients]

- Grade 3 infusion-related adverse reaction with 3rd dose (n=1)
- Grade 1 liver enzyme abnormalities (n=1)

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Conclusions

- Anakinra has moderate efficacy in treatment of ECD (overall response rate 50%)
- No responses seen with infliximab and etanercept
- Anakinra may be considered a treatment option in patients who are not candidates for targeted agents, especially milder cases and those without CNS disease

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Thank you

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