IL5, eGPA and therapeutic advances

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Disclosures

- Roche: Advisory board and speakers fees for rituximab,
- GSK: speakers fees for mepolizumab
- AstraZeneca speakers fees, Trial design commentary benralizumab
- Novartis speakers fees omalizumab

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eGPA

- Churg Strauss Syndrome, Allergic granulomatosis and angiitis

- 1-2/100,000

- UpToDate
  - Extrapulmonary involvement leads to morbidity
  - Actually steroids are much greater cause

Causes

- LTRA
- Inhaled steroids
- Omalizumab

- Just treating asthma and its really eGPA

- Cocaine (really is levimasole)
  - Elastase and occasionally pr3; C-ANCA pos
  - Skin necrosis is common, and nasal disease

Phases

- Like ANCA disease, this is a clinical phase
  - May have nothing to do with pathphysiology
- Prodromal: asthma, rhinitis
- Eosiniophilic phase: lung infiltrates

- Vasculitic phase:
  - None of my patients have had useful biopsies

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Disease is weird

- 46s F ANCA- Lung, asthma, cardiac, polyps
  - CYC, AZA, Mepolizumab
- 57s M ANCA+ lung, asthma, cardiac
  - CYC and AZA
- 55 F ANCA- Cardiac arrest, nerve, skin, CA
  - CYC, AZA, MMF, Rituximab
- 50 M ANCA+ Skin, asthma, muscle
  - AZA, MTX

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- 60 F ANCA- Lung, asthma, liver
  - MTX, AZA, oral then IV Cyc, SC Mtx
- 48 M ANCA- lung, asthma, ?cardiac, polyps, nerve
  - MTX
- 45 M ANCA+ Lung, nerve, asthma, polyps
  - CYC, MTX, MMF, MMF plus Xolair, MMF plus Benralizumab (asthma)

- 48 M ANCA- Asthma, myalgia, arthralgia, polyps
  - MTX, pred only
- 60 M ANCA- Asthma, CA
  - Pred only

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Overlapping disease definitions

- Eosinophilia is seen in multiple conditions
  - Atopy, eGPA, GPA, HIES, AERD
  - Some similar organ involvement
    - neuropathy
  - Asthma not always very prominent

- ANCA+ eGPA isn't the same as GPA/MPA
  - But induction should be

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Long term

- Glucocorticoid damage index high
  - Most patients remain on steroid

- Asthma can be biggest issue
  - Can respond to immune suppression
  - Biologics of use

Issues in management

- High burden of disease
- More than vasculitis
  - Asthma
  - Both contribute to steroid load
- Lack of clinical trials

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Vasculitis

- MPO pos in vast majority, also RF pos
- Does not have same clinical course as MPA
- Recurrent disease is the norm

- Most definite vasculitis is ANCA pos
- Cardiomyopathy less ANCA pos
- More renal disease (all ANCA pos)

Criteria 10% Eo

- Patients often evolve after treatment started
  - Making diagnostic criteria challenging
- 55 F ANCA- Cardiac arrest, nerve, skin, CA
  - CYC, AZA, MMF, Rituximab
  - 3/12 after CABG normal vessels
  - Intermittent eosinophilia only
  - Started MTX
  - Deteriorated
    - Skin involvement : explosions about veins

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- IV cyclo
- MMF
- Recurrent skin lesions and neuropathy

- Ritux 2 years
  - Relapsed
- Now maintenance

Treatment

- In UpToDate it says asthma should be managed separately
- I think this is totally wrong

- The asthma of eGPA is not the same as “normal Eo Asthma”

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Five factor score

- I think should be abandoned
  - Too many exceptions to it
  - Assesses prognosis, though may confound RX
  - ANCA+ disease, cardiac disease
  - In 90's FFS 1 or more 25-45% mortality 5 years
    - Probably cause only used steroids
  - Later series 10 year mortality 10 years
    - >70% cyclophosphamide

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IL-5 agents

- One has TGA/FDA registration
  - Not PBS listed for eGPA
  - PBS listed for Severe asthma
  - Mepolizumab (Nucala)

- At 300mg q4weekly SC

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RCT

- 136 patients one year
- Add on trial placebo vs Mepolizumab
  - Not new patients
  - 1) BVAS 0 with pred less 5 2) pred less than 7.5
- 44% tapered pred 5mg vs 7%
- 47% in mepo group no remission
- Used BVAS
  - Wheeze but no asthma control
  - Relapsed asthma only counted if hospital

No comparison with 100 Mepolizumab

- PB Eosinophilia at 300mg less than 150/uml
  - – 72%
  - -Eo's >150 works better
  - -53% achieved pred reduction less than 50%
  - -lots of possible reasons

  If pred >20mg no significant change but lacking power

  Only 20% ANCA pos in study, 10% baseline

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Critique of Summary

- Failure to see Eosinophilia is activity marker
- Messy patients
- Used BVAS
- Asthma control not assessed
- Experienced patients

- But still showed benefit to 50%

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Clinical experience

- Unpublished hearsay

- Given at 100mg asthma better
- Not enough experience re vasculitis

- One patient benralizumab for asthma
  - Better asthma

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What is coming?

- eGPA trial in benralizumab
  - Australia may be a centre
    - Though probably not
- Omalizumab: no
  - Mast cell agent only

- Multiple other agents in asthma
  - Non TGA listed

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The future

- Denovo patient trials
- Complex as need to combine treatments

- Ideally I think combo treatment with Bcell depletion and IL5 modulation might be best

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Il5 agent differences

- IL5 vs IL5 receptor
- Tissue eosinophilia
  - Relevance
  - FEG's and airway remodelling
- Il5 agents not immune suppressant
  - (parasite data unknown)

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Review of Ritux 2019

- 93% improvement at one year
- ANCA less airway disease, shorter time to relapse
- Ritux doesn't limit asthma or ENT well

- This was Addenbrookes
  - Biased patient population, pre-treated
  - 34% ANCA, 2/3 MPO 1/3 PR3

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Questions?

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