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
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
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
• 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
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
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
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
• 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”
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% cyclophosphamid
IL-5 agents

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

• At 300mg q4weekly SC
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
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%
Clinical experience

• Unpublished hearsay

• Given at 100mg asthma better

• Not enough experience re vasculitis

• One patient benralizumab for asthma
  – Better asthma
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
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
II5 agent differences

• IL5 vs IL5 receptor

• Tissue eosinophilia
  – Relevance
  – FEG’s and airway remodelling

• II5 agents not immune suppressant
  – (parasite data unknown)
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
Questions?