This presentation was presented at the 2017 International Vasculitis Symposium.

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The Vasculitis Foundation supports and empowers our community through education, awareness, and research.
International ANCA Associated Vasculitis Conference

“Diversity and Integration for Tomorrow” 2017

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• There were 451 abstracts presented from 29 countries at this year's conference.
• The main themes:
  • Classification of AAVs
  • Pulmonary limited MPA
  • Takayasus → GCA
  • Eosinophilic Granulomatosis with Polyangiitis (EGPA)
  • Therapeutic Updates
Classification Concerns

• We rely on autoantibodies (PR3 and MPO) to help guide us in classifying patients, enrolling in clinical trials, and to help us predict risk of relapse and which organs may be involved

• Easier $\rightarrow$ classic presentation/organ involvement, tissue diagnosis

• Difficult $\rightarrow$ overlapping features

• Genetic studies align more with autoantibody specificity (PR3, MPO) rather than the clinical syndrome and having specific genes can increase risk of relapse
Combining the serotype (MPO, PR3) and the clinical/pathologic phenotype will provide us with the most informative diagnosis. This will allow us to better categorize patients not just based on a blood test or pathologic finding or clinical picture, but rather use all this information in trying to understand the nature of these diseases.
Classification-Epidemiology

- UKIVAS (UK and Ireland vasculitis registry)
  - Longitudinal registry with over 3000 cases of vasculitis
  - Source for making comparisons between different countries
- ANCA testing → Earlier diagnosis, more clinical trials, improved survival and patient outcomes
- Must be vigilant about chronic damage and comorbidities

Registries such as this one will capture this important information so that we can better study vasculitis including damage from the disease and the therapies we are using to try and control it.
• Classification of AAVs

• Pulmonary Limited MPA

• Takayasus → GCA

• Eosinophilic Granulomatosi with Polyangiitis (EGPA)

• Therapeutic Updates
Pulmonary Limited MPA

• Types of lung involvement:
  • Hemorrhage
  • Interstitial disease
  • Bronchial disease

• Subset of patients with interstitial pulmonary disease and +ANCA → may go on to develop systemic vasculitis (average 4-5 years)
  • More likely with high titer MPO
Pulmonary Limited MPA

Understanding that patients initially presenting with lung disease (diagnosis of interstitial pneumonia) may go on to develop other systemic signs of vasculitis, helps us to watch these patients closer so that we can diagnose/intervene sooner.

Are there any clues or lab tests or imaging studies that can help us to identify these people?
Pulmonary Limited MPA

• Can be difficult to distinguish between vasculitis and fibrotic lung disease in MPO+ patients
• Inflammation vs Damage
• Interstitial Pneumonia (IP) is the primary pulmonary manifestation of patients with MPA and occurs in more than half of patients
• In the ANCA +IP patients, there is more honeycombing and cysts compared with IPF/UIP
• It can be dangerous to get tissue → no path clues yet
Pulmonary Limited MPA

- Limited GPA treated differently than systemic GPA
- Increasing reports of sole pulmonary involvement manifesting as UIP in MPA, not as a result of hemorrhage/local injury/fibrosis
- No clear treatment guidelines for MPA patients presenting with exclusively lung disease
- May go on to develop other disease manifestations
- May stay in the lung

There are multiple studies being carried out in various countries in patients who have lung disease or “limited MPA”. We need to see if we can better identify predictive factors in those patients who will go on to develop a systemic vasculitis or if they respond differently to therapeutic regimens targeting fibrosis.
• Classification of AAVs
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Takayasu $\rightarrow$ GCA: The Problem

• The delay in time to diagnosis is significant (258 days in TAK and 56 days in GCA) and there are overlapping features

• As a community, we are re-appraising the ACR classification criteria for Takayasu and GCA
GCA

- Age > 50
- Headache
- Polymyalgia sx’s
- High inflammatory markers
- Caucasians
- Females (2:1)
- MHC 2

Takayasu

- Age < 40
- Lower extremity claudication
- Damage/bruits
- Renal involvement
- # of vascular beds affected
- Asian/Turkish descent
- Females (9:1)
- MHC 1

MORE:

- Weight loss
- Fatigue
- Fevers
- Claudication
- Angiogram with stenosis
Takayasus $\rightarrow$ GCA

- How rigid should we be with our criteria?
- Japanese registry of “late onset Takayasus” (age >40)

By appreciating some of the differences in susceptibility, imaging findings and increasing awareness of the entity of late onset-TAK, we hope to decrease the time to diagnosis for patients who have these diseases and be better equipped to differentiate them so they can be studied closer in clinical trials.
Takayasu→GCA: The Treatment Experience and Options

• Steroids→prolonged and high doses

• Modest benefit of methotrexate in both diseases

• TNF inhibitors: looked promising in case reports but did not show benefit in RCTs

• Abatacept shown to be better than placebo at 12 months in preventing relapses in GCA, but this benefit was not seen in terms of relapse free survival in TAK
Takayasu → GCA: The Treatment Experience and Options

- Tocilizumab and IL-6
Takayasus → GCA: New Horizons

• GIACTA Trial: 250 patients from 14 countries with new or relapsing GCA

• Patients treated with tocilizumab did much better than the steroid only arm
  • More sustained remission
  • No increase in adverse events
  • Better QOL measures
There have been no new therapies for GCA in more than 50 years, and tocilizumab was just approved by the FDA. The landscape is truly changing and we hope to be able to improve the lives of our patients based on these trials with hopes of less or even possibly no steroids in the future.
Which patients are most likely to benefit?

At what point in a flare do we start it?

How long should we continue it for?

Can we use a lower dose?

Can we get patients off of steroids even faster?

Cost/Benefit??
• Classification of AAVs
• Pulmonary Limited MPA
• Takayasu's → GCA

• Eosinophilic Granulomatosis with Polyangiitis (EGPA)

• Therapeutic Updates
EGPA

EGPA is the rarest of the AAVs and is associated with late onset asthma, pulmonary infiltrates, neuropathy and peripheral blood eosinophilia

• About 1/3 have +p-ANCA
  • Those with the +antibody classically have vasculitic manifestations (neuropathy, skin)
  • Anca negative more frequently have cardiac manifestations, including cardiomyopathy or myocarditis
EGPA

• Disease course and response to therapy is different in EGPA → excluded from larger trials evaluating MPA and GPA
• We try cytoxan, azathioprine, and methotrexate to control the disease, but some of the manifestations such as chronic asthma or rhinosinusitis frequently require long term high dose steroids → resultant toxicities
• Environmental exposures in both asthma and EGPA trigger the immune system though cells in the airway secreting inflammatory cytokines

• This response also occurs in the cells lining the nasal cavity and can cause polyps or other ear, nose and throat involvement

• This results in further immune activation of the adaptive immune system
EGPA

• IL-5 is a cytokine that regulates growth, activation and survival of eosinophils and levels of IL-5 are increased in patients with EGPA and are associated with disease activity
EGPA

• Two pilot studies in EGPA with promising results
  • Steroid sparing effect
  • Remission maintenance
  • Favorable safety profile

• MIRRA trial, the first ever double blinded, placebo controlled trial in EGPA patients, to evaluate the efficacy of mepolizumab in relapsing and refractory EGPA

This means a possible medication outside of steroids, that is tailored to and targets the mechanisms that drive disease in EGPA

• Results will be available in late 2017
• Classification of AAVs

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MAINRITSAN: Follow up at 60 Months

• MAINRITSAN trial demonstrated that Rituximab was superior to azathioprine at maintaining remission at 28 months

• 60 month data → maintenance therapy with RTX remained significantly superior to AZA to maintain remission and was associated with better survival

• May be a role for ANCA monitoring to guide treatment duration
Mycophenolate vs Cytoxan for Remission Induction in Non-Life-Threatening Relapse

- Cytoxan is used to induce remission in AAV
- Mycophenolate mofetil (cellcept) can induce remission in non-life-threatening disease
- What about inducing remission for patients suffering from 1\textsuperscript{st} or 2\textsuperscript{nd} relapse?
Mycophenolate vs Cytoxan for Remission Induction in Non-Life-Threatening Relapse

• In patients with increasing disease severity, less MMF treated patients attained remission, whereas induction of remission with cytoxan therapy was unaffected by disease severity.

• Disease free survival was not significantly different at 4 years of follow up.

This means that MMF works well, is less toxic, and is a viable alternative to cytoxan in relapses of AAV disease if your organs are not affected in a life-threatening way.
WHERE
are we going?

IT’S A MARATHON,
NOT A SPRINT

6/30/17

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Acknowledgments

• Joyce Kullman, Executive Director of the Vasculitis Foundation

• Dr. Antoine Sreih, University of Pennsylvania

• My staff and collaborators in the Vasculitis center at The University of Chicago

• All of you
I DON'T KNOW WHETHER TO TAKE A NAP...

...OR CRY ABOUT BEING TIRED.
Classification-Genetic Markers

• Identifying genetic markers that confer increased risk for AAV
• No one gene responsible, but specific gene combinations can result in different protein expression in immune cells
• This can lead to higher frequency of T cells reactive to ANCA antibodies

By further studying the genetic etiology and variants in AAV, we may be able to influence and possibly predict clinical presentation of the disease, and target alterations in immune cell proteins that are critical in triggering the disease