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Decoding EGPA: A Clinical Deep Dive Into Diagnosis and Treatment

Announcer:
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Dr. Akuthota:
We will start by discussing the epidemiology of EGPA. Eosinophilic granulomatosis with polyangiitis is a rare form of vasculitis affecting about 5,000 Americans annually. From a global prevalence perspective, about 11 to 14 cases per million. This may be underestimated, but those are the best data that we have. The disease is most often diagnosed in middle aged patients, 35 to 50 year old with the history of new onset or worsened asthma. This is really the exception is more common than the rule. Patients can be diagnosed across a broad range from adolescents to later in life. Then from a comorbidities perspective, and you will see this when we talk about diagnostic criteria as well, many, many patients, most if not close to all patients, 85.5% of patients with EGPA had preceding asthma as well. From a gender distribution perspective, there is similar prevalence between males and females. Some studies report higher prevalence in women with an age adjusted prevalence from a 2018 study of 14.7 in females vs 10.8 in males. In general, it is a pretty even split between males and females for EGPA.

Systemic vs Respiratory Manifestations

Just as an overview of clinical manifestations. There is a group of manifestations that are systemic and then a group of manifestations that are in particular respiratory. Often you will see EGPA dichotomized into the respiratory and then to the systemic and extrapulmonary manifestations. I think the main message is that many organ systems, as you can see here from the graphic, can be involved in EGPA. From a respiratory perspective, the manifestations do indeed include those associated with asthma, dyspnea, cough, wheeze, but not just lower respiratory but upper respiratory as well.

The sinonasal disease is quite common. EGPA chronic rhinosinusitis with nasal polyps is often seen. Going back down into the lung parenchyma itself, the air spaces rather than the airways. There can be pulmonary infiltrates that are seen on imaging as well. These respiratory symptoms, particularly the asthma symptoms, often appear prior to other manifestations of EGPA. From a systemic perspective, there are many manifestations will go around the horn here on this figure. Systemic central nervous system manifestations can happen.

In particular, peripheral nervous manifestations, in the lower right are quite common, including peripheral neuropathy and classic mononeuritis multiplex. A few others that I would call out in particular are dermatologic manifestations. Often rashes with palpable purpura are seen. Intestinal manifestations may occur as well. We talked about ear, nose and throat manifestations. Renal manifestations, particularly, glomerular nephritis can occur as well. You can notice a theme here that some of these systemic manifestations are potentially driven by vasculitis, and have similar presentations or similar manifestations to other small vessel vasculitis. Then constitutional symptoms like fevers, weight loss, myalgias, and fatigue can occur as well. You will be able to look at this

slide as well at your leisure to remember what some of the various manifestations are in EGPA.

3 Stages of EGPA

From a disease course perspective, you will classically see written in textbooks that EGPA occurs in 3 stages, starting with a prodromal or allergic phase, which can potentially last for years, where people have antecedent, atopic disease, in particular asthma with or without chronic rhinosinusitis with nasal polyps. Potentially some other lurking systemic symptoms like fever, malaise, and that prodromal phase. This classic, description then will, evolve into an eosinophilic phase in which there is peripheral eosinophilia, often high grade, noted with tissue infiltration of various organs. Then that in turn will go into a vasculitic phase where there is organ threat based on vasculitis with granulomatous inflammation of various organs, not just the skin, but the kidneys and peripheral nerves, potentially the GI tract as well, with more constitutional symptoms.

As even though you will see, this written about a lot and I am talking about it here, this classic description is more often the exception rather than the rule. EGPA can develop in any pattern of these buckets of phases happening with various tempos and in then various mixes, so there is often not a strict linear progression through these phases and hopefully this graphic going back and forth between the boxes represents that well.

Role of Eosinophilic and IL-5

From a pathophysiologic perspective, as the name implies, eosinophilic granulomatosis with polyangiitis, eosinophils themselves have a important central pathophysiologic role in disease, in EGPA. Eosinophils are driven in their development from myeloid precursors all the way to migration into tissues and migration out of bone marrow and recruitment into tissues by IL-5. It is the most important cytokine that dictates eosinophil growth, development, survival, and movement.

You can see here on this figure, on the bottom in particular. As we will talk about in later sections, including Dr Wechsler section that is coming up next that targeting IL-5 can reduce eosinophil numbers often to zero. In IL-5 and IL-5 receptor targeting is an important modality in EGPA treatment using monoclonal antibodies.

Therapeutic Targeting of IL-5

This recapitulates some of what I just said. One can therapeutically target IL-5. You can see here on the left hand side of this figure, under normal circumstances, this is an eosinophil with the IL-5 receptor embedded in the plasma membrane. IL-5 binds to the alpha chain of the IL-5 receptor on eosinophils. That IL-5 signaling in turn promotes when IL-5 signals it to eosinophil precursors, signals the development to mature eosinophils and then also signals activation of eosinophils and recruitment of eosinophils into tissues.

Then on the right side of the screen here you can see, therapeutic targeting and how that may work. IL-5 itself bound by either mepolizumab and reslizumab to monoclonal antibodies against IL-5, which block signaling by binding up IL-5 and preventing its binding to its receptor. Monoclonal antibodies like benralizumab, which bind to the IL-5 receptor itself on eosinophils and then engage natural killer cells to cause direct killing of eosinophils through a process known as antibody dependent cell mediated cytotoxicity.

Role of Genetic and Environmental Factors in EGPA

From a pathophysiologic or mechanistic perspective and genetic perspective, EGPA is complex. It is not just driven by one thing. It is not a single gene driving EGPA that is seen in most patients with the disease. This is really a polygenic genetic disease with several potential genetic determinants that confer small levels of risk. Those include polymorphisms in the HLA. DRs, molecules. These are MHC class 2 molecules or in cytokine known as IL-10. There can be polymorphisms in that gene as well. These all confer small amounts of increased risk.

There is also an important acquired determinant patients. There is a gene by environment type process where patients over their life are exposed to various allergens, infections, vaccinations, drugs, other toxins that might help explain the development of EGPA. Then those in turn lead to dysregulated immunity in multiple levels, which you can see on the bottom of this graphic. Eosinophils themselves, which we talked about with IL-5, dysregulated T cell subsets, including Th17, and Th2 subsets. Th2, in particular driving atopic phenomenon. Then T regulatory cells not working as well to dampen inflammation of various types in these patients.

Then on the right, on the bottom, important issues or problems with humoral immunity as well as reflected by some patients being ANCA-positive, antineutrophilic cytoplasmic antibody positive, and that also these patients having elevated IgG4. Complex immunology that we are still trying to unravel from a mechanistic perspective that all go into determining development of EGPA.

EGPA Diagnosis and Classification

From a diagnosis and classification perspective, these are old criteria, but I think they are useful.

1990 ACR Classification Criteria for EGPA

There is not one set agreed upon diagnostic classification, but I think, using these old 1990 American College of Rheumatology criteria can be useful because they tell us that EGPA is really a syndrome, a diagnosis, not a pathologic. Necessarily a pathologic diagnosis. biopsy can help. It can help make the diagnosis, but it is not necessary to make the diagnosis. Similarly, ANCA, which is not on this diagnostic schema, can help make the diagnosis but it is not necessary to make a diagnosis. Many patients are Anca negative.

In this old 1990 classification criteria, patients needed to have 4 of the following criteria asthma, eosinophilia, neuropathy, pulmonary infiltrates, paraspinal sinus abnormality or indeed a biopsy. All other diagnostic schema that you will see, we are not going to go over in too much detail, but they all rely on a syndromic criteria based diagnosis rather than necessarily needing a biopsy and or a positive ANCA to call a patient as having EGPA.

2022 ACR/EULAR Classification Criteria for EGPA

These are the 2022 American College of Rheumatology/EULAR classification criteria for EGPA. This is a different set of criteria that are used in the rheumatology community, that are used in patients that you already know have vasculitis. If you have a sense based on clinical and serologic criteria evaluation that a patient has a small or medium vessel vasculitis, you can use this scoring system to say that somebody has EGPA or not. You get these points on clinical and lab criteria. If you have a score of greater than or equal to 6, that will give you a diagnosis of EGPA. Obstructive lung disease, nasal polyps, mononeuritis multiplex. These give you points. A high blood eosinophil count. This gives you a lot of points. A positive c-ANCA or an anti-PR3 antibody. This takes off points because that is more likely to be another ANCA associated small vessel vasculitis like EGPA.

ANCA Status in EGPA

Speaking of ANCA status in EGPA, about a third of patients with EGPA by many case series are ANCA positive. ANCA positive patients tend to but do not exclusively have more tendency toward vasculitic phenomenon, including glomerulonephritis and peripheral neuropathy, including mononeuritis multiplex. Then the ANCA negative patients tend to have more eosinophilic type uh mediated pathology, including cardiac and pulmonary involvement. These are not exclusive disorders between particular manifestations exclusively going toward ANCA negative and or exclusively going toward ANCA positive. There is a lot of overlap here.

Patient Case 1: Mrs. Stacey, 48-Yr-Old Woman

Let us talk about a patient case briefly. This is Mrs. Stacey, a 48 year old woman who presents to the emergency department with worsening shortness of breath and chest tightness. She reports having burning pain and weakness in her left foot for a week. She reports fatigue, migratory joint pain, and new red, painful rash on her legs. She has a past medical history of asthma diagnosed over a decade ago, worsening over the last 2 years. Nasal polyposis with multiple surgeries, allergic rhinitis, sinusitis and hypothyroidism. You can see her vital signs there. Significant findings include an oxygen saturation of 95% on room air. On exam, she had a decreased sensation in her left foot with a foot drop. She had bilateral nasal congestion on ENT exam with crusting. Her significant labs included an absolute eosinophil count of 44,340. High CRP and ESR. Creatinine above baseline of 1.3. Some proteinuria on her urinalysis with microscopic hematuria, and positive p-ANCA, which was MPO or myeloperoxidase, antimyeloperoxidase positive. Then she had a negative ANA and she had an elevated IgE.

I will talk about this case a little bit with my colleagues in a moment. When you are evaluating a patient, like was done in this case, there are many test you can use based on specific information provided to evaluate patients with EGPA. Here is a list here. I am not going to go through all of them, but some routine lab findings, serologic findings for systemic inflammation can be helpful. Organ specific routine labs, immunologic testing for immunoglobulins as well ruling out infectious disease, particularly parasites. Other hematologic tests to look for hypereosinophilic syndromes and then other imaging tests directed at organs, particularly chest imaging and echocardiogram. Just to throw it to my colleagues who I can introduce as they jump on camera, what diagnostic tests do you routinely use in your practice to confirm a diagnosis? Let us start with Dr Anisha Dua from Northwestern University.

Dr. Dua:
Hi, everyone. Thanks for asking. I think it is really based on what the person is coming in with. With this patient who is having nasal crusting and obviously some neurologic symptoms, I would definitely do a neurologic workup. Neuropathic involvement for me is a really big clue for underlying diagnosis of EGPA. In terms of biopsies and stuff, I do pursue them, especially of the skin, when you have got active skin lesions. The crusting is a little bit confusing because that can go a little bit. Make me think about some of the other modalities like GPA and MPA, especially with that positive MPO and p-ANCA. I would have done some of the workup that is already been done, but in terms of further diagnostics, I definitely start looking at the organ manifestations that the person's coming in with and deciding whether they need biopsies or fill that clinical syndrome that you were talking about.

Dr. Akuthota:
Then Dr Michael Wechsler from National Jewish in Denver. Hello.

Dr. Wechsler:
Hi. Great to be here. Thanks for having me. I think for me, one of the main components of diagnostic workup is to evaluate for things that could be confusing with EGPA. Making sure that you exclude infection, making sure that you exclude malignancy, making sure that you have seeked out alternative diagnoses that could be either eosinophilic in nature, drug reactions, and whatnot, or vasculitic in nature. You want to go to the organs that have clinical manifestations and target them whether it is by imaging, whether it is via biopsy, or serologically. You could also consider alternate testing, for instance, echocardiogram and cardiac MRI as part of the evaluation for cardiac manifestations, EMG nerve conduction studies for neurologic manifestations.

Dr. Akuthota:
Fantastic. Thanks. I will see you both in a little bit here.

Role of Biopsy in Diagnosing EGPA

All right. I am going to quickly go through a couple of more slides. I am going a little long and I will pass off to my colleagues, but the role of biopsy in diagnosing EGPA I think I have already said is not essential to make a diagnosis. If feasible, we recommend that you do it and that will be, organ specific based on where somebody's disease is manifesting itself. That could be ENT. It could be a lung biopsy. could rarely be GI tract often skin, often nerve, sometimes kidney as well if somebody has an active urinary sediment.

Patient Case 1: Mrs. Stacey, 48-Yr-Old Woman Laboratory Assessment

All right. We just looked at this case a moment ago, and we are going to focus in on that. The skin biopsy in this case which is added information, reveals necrotizing small vessel vasculitis with an eosinophil rich infiltrate. In this case, a biopsy help make the diagnosis of EGPA. Though is not always necessary.

Poll 3

Let us go with the polling question here. Which of the following clinical features is most strongly associated with ANCA positive EGPA?

A. Cardiomyopathy;

B. Alveolar hemorrhage;

C. Nasal polyposis;

D. Eosinophilic pneumonia, or

E. Gastrointestinal involvement;

I will give you a second. All right. Let us see what people said. Very widespread on the polling question and let us look at the answer here. Alveolar hemorrhage, which is a very vasculitic manifestation, is more strongly associated with ANCA positive EGPA. That is something to remember.

Faculty Discussion

All right. I think we did a lot of discussion already. Maybe we will put a pin in these and talk about them at the end. Just to, talk about what some of the questions might be. What red flags prompt EGPA? How do you differentiate EGPA from other hyper eosinophilic conditions? What role does ANCA testing play? Which organ involvement is most frequently to diagnosis of EGPA? That is all food for thought for the end of the program.

Posttest 1

We will do these posttest questions as well. You have seen these. I will not read them fully, but this first one. This patient had adult onset asthma, purpuric rash, eosinophil count of 3,200, ANCA positivity. She had mononeuritis multiplex, and which pathologic process most directly explains the patient's neuropathy and renal findings? Go ahead and answer. Let us see the responses. We are starting to triangulate a little bit more on the answer of C, Th2 cytokine-driven eosinophilic inflammation. I am not sure if Th1 inflammation or Th17 mediated neutrophilic inflammation is also very important in vasculitic manifestations as well. There is a lot going on in EGPA, but for here, we have given you Th2 cytokine-driven eosinophilic inflammation.

Posttest 2

The second post-test question. This patient we were talking about the EULAR score. Which single additional finding would most

increase this patient's EULAR score?

A. Hematuria;

B. Negative PR3;

C. Nasal polyps; or

D. Elevated total IgE;

Let us see the answer. People said hematuria. It is a pretty widespread here as well. The only thing here that gives you positive results is the nasal polyps on endoscopy. The negative PR3 and ANCA does not give you positive, numbers, but it avoids a negative score on the EULAR scoring. All right. Then finally the last one. We do not have the last one.

Recent Advanced in EGPA Treatment

Now I am going to pass it off to Dr Wechsler, who will be talking about recent advances in EGPA treatment.

Dr. Wechsler:
Hello. Let me rejoin here.

Dr. Akuthota:
Off camera as you go on. There you go.

Dr. Wechsler:
Perfect. Thanks so much, Praveen. Great to be here with you all again. I am Mike Wechsler from National Jewish in Denver, Colorado. One of the most exciting things about EGPA is the fact that we have had so many advances in the management of EGPA just in the last couple of years, and it has really revolutionized the way we manage our patients with EGPA. What I will do is I will go through some of the past and future therapies and some of the new guidelines that have emerged over the last couple of years.

Currently Available Therapies

Here we go. Sorry. It seems like the slide thing is having a mind of its own. First of all, in terms of currently available therapies, we generally think of treating EGPA with systemic glucocorticoids and cyclophosphamide. Those have been used historically for remission induction. The last decade or so there has been addition of rituximab as part of that based on other studies and vasculitis, other vasculitides, including GPA, where rituximab was shown to be effective in terms of inducing remission.

Alternative options that have been used historically include other disease modifying rheumatologic agents, including methotrexate, azathioprine, and mycophenolate. However, the only 2 approved therapies for the management of EGPA include the anti-IL-5 agents mepolizumab and benralizumab. Review these therapies and some of the studies that led to their approval in EGPA, as well as some of the guidelines.

Comparing Guidelines for Nonsevere EGPA

In terms of guidelines, they are not completely updated. They have not been updated in a few years. However, there were some guidelines established in 2021 by the American College of Rheumatology and in 2022 by the European League Against Rheumatism. For active non-severe EGPA, the ACR guidelines advocate for utilization of glucocorticoids with mepolizumab or methotrexate, azathioprine or rituximab. Again, these are for patients with active non-severe EGPA. We are talking about non-severe. We are talking about non-life threatening and non-critical organ threatening disease.

For management of patients who have relapses and who have been treated with methotrexate, azathioprine, or any of the other agents. The recommendation is to add glucocorticoids and mepolizumab. For nonsevere disease relapses after mepolizumab or rituximab, then one should consider other immunomodulatory approaches because those patients are obviously not responding. The 2022 EULAR guidelines evaluate patients again if they have non-organ, life threatening disease and active EGPA. Then recommendations start mepolizumab. This was before the approval of benralizumab for this indication. If they are not relapsing and or have refractory disease, then one could consider. If they are relapsing or having refractory disease consider adding glucocorticoids. The goal of glucocorticoid management is to try to get patients down to as low a dose as possible so as to prevent many of the side effects of glucocorticoids.

Comparing Guidelines for Severe EGPA

When we look at the comparison of these 2 sets of guidelines, there are some differences that are a little bit nuanced in terms of induction, maintenance, and use of glucocorticoids, as well as for management of relapses, but in general for more severe disease. For severe EGPA, the recommendations are to utilize glucocorticoids with either cyclophosphamide or rituximab. Then for maintenance

therapy to switch to methotrexate, azathioprine, or mycophenolate and consider mepolizumab in the 2022 EULAR guidelines. The goal is to try to taper down glucocorticoids in all these patients. Getting down to as low a dose as possible. For management of relapses of these patients with severe disease, it is recommended if the patient was not receiving rituximab than to consider using rituximab. There are not data for the anti-IL-5 therapies because they were not tested in this patient population. Much of the data in for severe EGPA is based on the rheumatology literature for other vasculidities.

MIRRA: Remission and Relapse With Mepolizumab

The data resulting in the approval of mepolizumab, the anti-IL-5 therapy that reduces eosinophils, is based on the MIRRA trial. This was a study looking at mepolizumab, an anti-IL-5 therapy that was previously approved in asthma in patients with relapsing or refractory EGPA. Patients were randomized to receive 300mg of mepolizumab, which is different from the 100mg dose for up to a year. It was demonstrated that when we looked on the left hand side, the proportion of patients who are in remission, you can see the odds ratio of going into remission, which was defined as having a Birmingham Vasculitis score of zero and being on 4 milligrams or less of prednisone.

You can see that the odds ratio is 6 times higher with mepolizumab compared to placebo. When you look at the relapse rate in this patient population, again, a relapsing or refractory population, the time to relapse was significantly increased with mepolizumab and the rate of relapses was cut in half by about 50%. Mepolizumab was safe, well tolerated, resulted in significant reduction in relapses, significant increase in the proportion of patients who were able to achieve remission.

Real-world Data of Mepolizumab in Patients With EGPA

Some real world data have been published on the left hand side, with 100mg of mepolizumab. On the right hand side with 300mg of mepolizumab, and you can see that when you follow these patients in the real world treated with mepolizumab, there is a significant proportion of patients who are able to achieve quite a good response. Let us focus on the FDA approved dosing of 300mg every 4 weeks. You can see that by 6 months, close to 70% of patients had a partial or complete response. That proportion increases such that by 24 months, 92% of patients achieve a partial or complete response. This suggests that there is significant efficacy with targeting IL-5 and targeting the eosinophils.

MANDARA: Time to Relapse With Benralizumab vs Mepolizumab

The MANDARA trial was a head to head comparison between benralizumab and IL-5 receptor antagonists with mepolizumab and anti-IL-5 therapy. What we did was we administered 30mg of benralizumab monthly or 300 mepolizumab monthly, and demonstrated that benralizumab was noninferior to mepolizumab in terms of the proportion of patients who ended up relapsing and the proportion of patients who ended up going into remission.

MANDARA: Oral Glucocorticoid Reduction (48-52 Wk) With Benralizumab vs Mepolizumab

Another important feature of this clinical trial was the glucocorticoid sparing that was observed with both benralizumab and mepolizumab. When we looked at the proportion of patients who were able to reduce their corticosteroid dose by 50% or more at baseline, you can see that mepolizumab reduced 74% of patients receiving mepolizumab, and 85% of patients receiving benralizumab were able to cut their steroid dose in half or more.

When we look at 100% glucocorticoid withdrawal, so people able to come off of glucocorticoids, 41% of benralizumab patients and 26% of mepolizumab patients were able to come off of glucocorticoids completely. 70% of patients, close to 70% were able to get their glucocorticoid dose down to 4 milligrams or less. Really important reduction in exacerbations. Prevention of relapses, getting patients remission and off of glucocorticoids.

Emerging Treatment Options

Those therapies have just emerged in the last couple of years approved by the FDA, but there are also several other therapies that are. Depemokimab is a long acting anti-IL-5 therapy that has been in development now for both asthma and EGPA. Results of this study should be available next year, but this therapy is anti-IL-5 that is administered every 6 months. Imagine that taking twice a year therapy to block your eosinophils. Tezepelumab blocks TSLP or thymic stromal lymphopoietin. Already approved in asthma. It is undergoing a study in EGPA as well. NS-229 is a JAK inhibitor that works a little bit further downstream on all the type 2 cytokines and more, and may be beneficial in patients with EGPA.

Patient Case 2: Mr. Samuel, a 55-Yr-Old Man

Let us take a quick look at a case. Here is Mr. Samuel, a 55 year old gentleman who had moderate, persistent asthma, nasal polyps, and his respiratory symptoms became worse and worse. He presented to the outpatient clinic, stating that in addition to worsening

respiratory symptoms, he had bilateral foot numbness and weakness, and this results in difficulty walking. He also had a painful red rash on his shins, fatigue, myalgias, fevers, shortness of breath. However, he did not have any new infiltrates. In addition to his past medical history of type 2 diabetes, he was found to have marked eosinophilia. Eosinophil count of 4,000 with elevated inflammatory, sedimentation rate, and CRP markers. Positive p-ANCA again myeloperoxidase positive. Normal renal function. No urinary abnormalities. A skin biopsy that showed leukocytoclastic vasculitis with eosinophilic infiltration. He had nerve conduction studies that showed mononeuritis multiplex. This is a very typical case, meaning all the key features of EGPA. He had no cardiac or renal involvement. Initial workup and he was diagnosed with ANCA positive EGPA.

Poll 4

What is the most appropriate therapy for Mr. Samuel at this point?

A. Oral prednisone, 1mg/kg a day;

B. Prednisone with methotrexate;

C. Prednisone with cyclophosphamide; or

D. Mepolizumab monotherapy;

Take a moment to answer. Let us see how people did. Interestingly, a lot of people wrote mepolizumab monotherapy. However, in this patient who had acute presentation of EGPA, you really want to get the patient under good control. I think the appropriate response would be prednisone with cyclophosphamide for this type of patient. Mepolizumab has not really been tested in the acute setting. Presentation of patients with EGPA. There we go. At least I got it right.

Patient Case 2: Mr. Samuel, a 55-Yr-Old Man Follow-up

All right. Next. During follow up at 8 weeks, his asthma is better controlled, his skin rash resolved, and his neuropathy plateaued. However, he had significant insomnia and worsening glucose control. How do you interpret this information?

Poll 5

Probably as a result of some corticosteroids, what is the next appropriate management for him? Would you

A. Taper his prednisone rapidly;

B. Switch from cyclophosphamide to azathioprine;

C. Add mepolizumab and taper cyclophosphamide;

D. Discontinue all immunosuppression and monitor;

Take a moment to answer. Let us see how people did. Here, a lot of people said add mepolizumab and taper cyclophosphamide. I actually think that adding mepolizumab is not a bad answer, but I think switching from cyclophosphamide to azathioprine is currently the standard of care for these patients. You do not really taper the cyclophosphamide. You want to get people off of cyclophosphamide to try to prevent long term complications. Obviously, tapering prednisone rapidly can result in worsening of his underlying disease and discontinuing all immunosuppression and monitoring could be a problem as well. I think the answer here ought to be switching from cyclophosphamide azathioprine. Mepolizumab could be an option as well, but I do not think I would taper the cyclophosphamide necessarily.

Faculty Discussion

Let us get my colleagues on the line here. Let us have a quick discussion. Let us do a rapid fire with you guys. Praveen, let me start with you. For a patient like Mr. Samuel, the 5 factor score of one due to neuropathy, what factors push you towards cyclophosphamide vs rituximab?

Dr. Akuthota:
That might be a better question for Anisha, but I am not using the 5 factor score super often. I think refractory renal failure might push me towards cyclophosphamide over rituximab. Again, I am going to check it out and see what Dr Dua has to say.

Dr. Wechsler:
You can use the phone a friend option.

Dr. Akuthota:

Yeah, I am phoning a friend on that one.

Dr. Dua:
Thanks, Praveen. I am your friend. I think that there is decent data for both cyclophosphamide and rituximab with patients with an elevated 5-factor score. I think, with neuropathy, either are reasonable to use. There is more recent data from the RIO VAST trial that compared both of these agents in patients with an elevated 5-factor score so severe organ involvement which includes mononeuritis multiplex, and cardiac involvement and all those other things. I think it is reasonable to use either of these agents. I have been leading more lately towards using a lot more rituximab after the RIO VAST were published. I think ACR guidelines say to use cyclophosphamide in cardiac cases and EULAR guidelines there is a little bit of differences. I think you can use either, and both of those societies support have evidence for both drugs.

Dr. Wechsler:
Sounds good. Sounds like you will not be faulted for trying either one. At what point would you consider transitioning from induction to maintenance therapy, and which agents do you prefer once you are switching?

Dr. Dua:
I will just keep going with that for a second. If I am using cyclophosphamide, I will use about 3 months of it. If they are doing stable, then I will switch them over to their maintenance therapy. If I am inducing them with rituximab then I would switch over at the 6 month mark. I might consider if I am using rituximab upfront. If they do well to continue rituximab, there is some data that will be coming out slowly about rituximab as a maintenance agent and that is starting to be presented. If I am switching them over to a DMARD, I usually will switch them over at around the 3 month mark if they are doing well. I would usually use either azathioprine, methotrexate, something like that. I will sometimes add mepolizumab, especially if they have some of those eosinophilic or Th2 manifestations if I can get it approved.

Dr. Wechsler:
Why not add mepolizumab? Go down to the third question there. When you add Mepolizumab or switch to mepolizumab.

Dr. Akuthota:
Why not? Indeed. I think, you do not necessarily have to feel like you are strictly in the maintenance phase before you add it. I think you can you can start it on the earlier side. And that is perfectly reasonable.

Dr. Dua:
I agree that it is totally reasonable to do. I think the coverage is the hard issue when you are trying to get 2 biologics covered. If you are doing rituximab against mepolizumab from a functional standpoint can be hard to get approved. I think there is like pathophysiologic data that definitely shows it would be helpful. I usually do not use that as a maintenance agent after severe disease in most cases just based on the guidelines, which I do not totally agree with and they are based on mediocre data.

Dr. Wechsler:
Not necessarily even in EGPA. Is there a potential role for using the anti-IL-5 agents up front even before or instead of cytotoxic therapy? What do you guys think? Praveen?

Dr. Akuthota:
I would say probably yes. We need to have evidence generation around that. I think, the asthma and COPD literature are starting to suggest that you can give IL-5 receptor therapy in acute settings. Perhaps, that might be a viable strategy to generate some evidence around in the future for EGPA patients but we are not there yet. I think it is a good hypothesis.

Dr. Wechsler:
Sounds good. Any other thoughts, Anisha?

Dr. Dua:
Yeah. Patient profile wise, definitely a non-severe disease. There is good data there so in patients who do not have an elevated 5 factor score, I think there is definitely data to support using mepolizumab upfront.

Role of Immunosuppressive Agents in EGPA

Dr. Wechsler:
Sounds good. Let us just transition here briefly to the role of some immunosuppressive agents in EGPA, including for severe EGPA we have already talked about cyclophosphamide and rituximab, particularly in patients who are ANCA positive. There may be a role there. For remission maintenance, azathioprine, methotrexate, mycophenolate, and rituximab have been utilized. For nonsevere EGPA, there are some data supporting use of those agents for remission, but they are not used in necessarily in routine clinical practice. The anti-IL-

5 tend to be utilized more now for nonsevere EGPA. I think we have to balance what we know, what has been in clinical trials in EGPA with historical remnants from other vasculidities and not be necessarily bound by the history and consider more what the potential benefits are and potential risks as well. These are all important questions I still think need some answers.

Posttest 3

Let us just go on a couple of quick cases here. 43 year old woman with adult onset asthma, rhinosinusitis nasal polyps, prior biopsy showing eosinophil predominant small vessel vasculitis, has relapsing non-severe EGPA and is taking prednisone 15mg a day and methotrexate 20 a week, but flares when prednisone gets down to less than 10. Her eosinophil count of 1700. She is ANCA positive. PR3 negative. Would you

A. Increase methotrexate to 25;

B. Start anti-IL-5;

C. Switch to azathioprine and hold biologics;

D. Begin rituximab with pulse methylprednisolone;

next. Let us see what you guys think. Some of you said begin rituximab with pulse methylprednisolone. Some of you said start anti-IL-5 therapy. I think these are reasonable, choices. Again, she has been doing well. On current standard therapy, this is the exact type of patient that was enrolled in both the MIRRA and MANDARA trial. These are patients who would benefit from anti-IL-5 therapy. She flares. She has relapsing disease. That has been difficult to taper down, and it would allow for steroid withdrawal. In this case, I would go with anti-IL-5 therapy. I am going to pass the baton on to Anisha. Anisha Dua, welcome.

Partnering With Patients to Achieve and Maintain Remission in EGPA

Dr. Dua:
Thanks, Mike. In the last few minutes here, I am going to talk a little bit about partnering with patients in terms of achieving and maintaining remission in EGPA.

Burden of EGPA

We have talked about all the different disease manifestations and the burden of EGPA can really be very severe multi-organ involvement resulting in a lot of glucocorticoid use with all of the side effects that we all know we are trying to counsel our patients on and manage. A lot of asthma exacerbations which land patients in the ER, as well as hospitalized. This really drives up healthcare utilization costs. The fact that we do not recognize this disease early can also contribute to this burden. Because the longer you wait to try to treat that inflammation, the more damage that is accruing and the more lack of access to the medications that need to be implemented happens.

Patient Perspectives on the Burden of EGPA

There have been a couple of interesting studies looking at the patient perspective on the burden of EGPA. There was a qualitative interview of adults in the MANDARA trial that had EGPA and they reported more than 35 symptoms reported as bothersome. That is a lot of different symptoms. All of these patients reported trouble with breathing and shortness of breath. Most of them reported coughing, wheezing, neuropathy, fatigue, and nasal congestion and discharge. You can imagine that having all of these symptoms can lead to significant impact on your ability to function as a regular human, to work, to exercise, to sleep well, to engage in social activities. It is just really showing the patient perspective on how frustrating whether it is life or not life threatening the disease can be in terms of their functioning.

There was another exploratory study using social media that found that a third of patients with EGPA had significant issues with diagnostic delays and misdiagnosis. The reason that is really important is because if we are unable to recognize and diagnose these patients, then we cannot get them on the appropriate treatment, and we are treating them with multiple courses of steroids. Again, with those resultant side effects. If we cannot get that diagnosis, then it is hard to access a lot of the newer medications that have now been shown to really help control this disease in these patients.

Symptom Burden of EGPA

This again, is just a picture of how the symptom burden in EGPA can really be significant and diffuse. You can see the numbers and I will not go through them. Constitutional symptoms like skin manifestations, GI, respiratory, ENT, cardiovascular, neurologic, other, and a lot of these bars go all the way to the end. You can see the percentage of patients reporting many of these different symptoms is really, really high. I think it is just important to note how multisystemic this disease is, and depending on what perspective you are or what type

of provider you are, you might be dealing with different pieces of this. From a patient perspective, their whole body can be involved. I always tell people with small vessel vasculitides we have small blood vessels everywhere. Any of them can be affected and can impact your quality of life.

Shared Decision-making in EGPA

When it comes to having these burdens, you really want to leverage the patient perspective and what is bothering them the most in terms of deciding how to pursue treatment and how to talk to them about what treatments make sense for them. The best way to do that, of course, is to communicate with them and see your patients and talk to them about, what is bothering them and what the different pros and cons of different medications would be? How they are monitored, how they are administered, and talk to them about what they really value. Make it relate to their actual life and their functioning limitations to help them see why these immunosuppressive medications or steroids which have a lot of side effects potentially can really improve their quality of life. What makes sense for them in terms of their frame of reference.

Once you do that conversation and really explain it to them, then they are much more likely to stick with that therapy and that regimen, and you come up with how you are going to follow up, what labs are going to be needed, what types of imaging studies, or different types of studies, PFTs, etc., are going to be needed to really monitor their disease? That is really important and critical in terms of doctoring these patients and making sure that they feel like they are weighing in on that entire process and understand the benefits of these treatments that they probably have not heard about, They have not had friends that necessarily have this diagnosis. It can be a scary place for a patient to be. It is just important to remember, as a provider to be able to connect with that lack of information and be able to give it to them in a meaningful way.

Risks and Benefits of Glucocorticoids

Risk and benefits of glucocorticoids. Again, I know we do not have much time left in this talk, so I will not go through these because I do feel like we really understand them quite well as providers. We use a lot of steroids. It is a double edged sword. They work really well in terms of controlling inflammation, but they have a boatload of side effects which are listed here. here are many challenges that all of us have dealt with in our patients who are on these chronic glucocorticoids, ranging from severe things like new onset diabetes with wound ulcerations and hip fractures, as well as other things that might not be quite as severe in some ways, but also very life limiting in terms of trouble sleeping, agitation, difficulty focusing, and we are all pretty familiar with those.

Management Strategies for Comorbidities

How do we manage this beyond figuring out what the patient specifically needs and working with them to minimize those comorbidities? We want to obviously monitor for treatment related adverse events, try to preserve their organ function to improve survival and reduce mortality, which has been a really improved in the last 10 years. With the new trials actually focusing on EGPA patients. Regularly monitoring for disease prevention or progression preventing infection. Because we know as we use these drugs, they can increase the susceptibility to infections, and also the disease itself increases susceptibility to infections. Then managing peripheral neuropathy can be a really, really tough one for patients to deal with and manage because those symptoms can really last very long and be quite debilitating. Ask them about their psychological and lifestyle needs. What do they do in terms of social support? What do they do in terms of work, and how can you help make those specific components more functional for the patient?

Multidisciplinary Care Pathways

This is not something that you are solely responsible for. They need to have a team, and that is why a lot of vasculitis care happens in some of these specialized centers. It can be difficult when you do not have access to some of these centers. Because these diseases are so multi-organ, it is really important to have other people on board helping to monitor some of the other manifestations of the disease. You can see that a lot of these different specialties are listed here and again will not go through all of them in detail.

Patient Case 3: Ms. Martin, a 43-Yr-Old Woman

We will go quickly to a case. Ms. Martin is an elementary school teacher. She has persistent asthma and nasal polyps for several years. She began feeling overwhelming fatigue, developed a painful rash and lost sensation in her right foot. She could no longer stand comfortably in the classroom or keep up with her young students. After weeks of bouncing between specialists and rheumatologists, ordered the right labs. Yay, rheumatology and a biopsy, and her labs showed an elevated eosinophil count. Positive MPO-ANCA. Mononeuritis multiplex biopsy proven eosinophilic vasculitis. She got the diagnosis of EGPA. She was started on prednisone and 1mg per day, along with oral cyclophosphamide, with close monitoring by a multidisciplinary team. The early days were difficult nausea, insomnia, and the emotional weight of the diagnosis.

Patient Case 3: Ms. Martin, a 43-Yr-Old Woman Follow-up

Now she comes to follow up. Three months later, her rash faded, her breathing improved, and her blood counts normalized. She was still on low dose prednisone and ready for the next step. She and her rheumatologist discussed options, and she was hesitant about long term steroid use. Reasonably, talking about her weight gain and her mood swings and how they were really negatively impacting her life.

Poll 6

Now she has completed 3 months of induction therapy with prednisone and cyclophosphamide. She is in clinical remission and expresses concern about the steroid use. What should we do next? The options are

A. Continue prednisone and cyclophosphamide for another 3 months;

B. Discontinue all treatment and monitor for relapse;

C. Begin mepolizumab and taper off prednisone;

D. Switch to methotrexate and maintain prednisone at 5 milligrams a day; or

E. Replace prednisone with azathioprine and stop cyclophosphamide;

I know the poll has been sent out. I will give you just a few seconds to answer it because we are out of time. All right. You want to go in advance. The majority here said begin mepolizumab and taper off prednisone with a little bit of a spread between some of the other options here. That is correct, but you want to begin mepolizumab and taper off of prednisone because she is having a lot of those side effects and she is ready for switching over to her maintenance agent.

Faculty Discussion

I do not know that we have necessarily time for some of these discussions. I will ask maybe each of you, if you guys want to come on camera, one of them, and then we can move on. Praveen, you are on camera. I will just do the first 2. How do you tailor steroid tapering in patients with EGPA and early signs of steroid toxicity? How do you approach the issues that come up early on when patients are having all these steroid related issues?

Dr. Akuthota:
I think, it is a tricky issue. First of all, with steroid tapering, I feel like you taper as quickly as possible as symptoms allow. I do not go necessarily with the cookbook to try to eliminate some of those or limit some of those steroid toxicities. Especially with early signs of steroid toxicity, that should be, again, another kick toward trying to taper as aggressively as possible. Sometimes that means putting adjunct agents on as well, that you might not have started that early. That is the basic.

Dr. Dua:
No, I think that is fair. Mike, I will ask you the second one. This is a really tough one actually. Persistent neuropathy post treatment. How do you distinguish between damage vs active disease? I think this is something that comes up a lot in clinical practice. How do you approach that?

Dr. Wechsler:
I think it is important to work with neurologists and also utilize some objective criteria from EMGs and nerve conduction studies, and evaluate whether or not there has been progression over time. Sometimes it is just damage that is just going to persist and persist. The patients will complain. You just have to try to reassure them that as long as things are not progressing and not getting worse then they should be ok. Things might slowly get better.

Dr. Dua:
I totally agree. I think that is one of the things that is the slowest to improve and it takes so long but you can see it. It just requires a lot of patience and medications to control the pain. I will move on because again with time.

Posttest 4

Posttest question, how confident are you in your ability to integrate shared decision making in the management of patients with EGPA?

A. Not confident;

B. Somewhat not confident;

C. Somewhat confident;

D. Confident; or

E. Very confident. I will give you 5 seconds. Go ahead. We have moved up a little bit. We have more somewhat confident and a little bit of confident even so that is great. Nobody is not confident and that is important. I will go to the next one.

Key Clinical Takeaways

The real key takeaways here and I know we covered a lot of data, is that EGPA is a rare disease. It is challenging to diagnose and manage because it can present in so many different ways with different levels of severity. It has a really large burden on patients. It affects their physical health, their emotional health, their quality of life, and just their everyday functioning. Whilst glucocorticoids really remain a major cornerstone of EGPA treatment, we know the many issues that can come with using these short and long term. Agents that are targeting IL-5 in clinical trials really focused on EGPA, which is wonderful because many of the other trials have not have demonstrated efficacy and safety in the treatment of EGPA. They allow us to really reduce or discontinue systemic glucocorticoid therapy.

Question and Answer Session

In terms of questions and answers, I think, there was some question in the box in the Q&A and I think it was answered in that area. It was just about, how long to wait after rituximab before starting mepolizumab? Would you check a CD-19 or 20 level first? Praveen responded to it. I do not know if you guys can see that, but he said he personally starts at 6 months and not based on CD-19 or 20 count. I agree. I do not really follow the CD-D0 count for deciding when to reduce rituximab. In terms of initiating mepolizumab, I do not think you necessarily need to wait till the 6 month mark at all to start it in really sick patients where I am inducing them with rituximab, I might use mepolizumab upfront. Again, it has more to do with insurance coverage than it does with what I think the impact on the disease would be.

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