



## Inside the Doctors Studio – Retina nAMD

### Retinal Physician Supplement

In the most recent podcast episode of Inside the Doctors Studio - Retina ([Click here to view CME information and claim credit](#)) vitreoretinal specialist Arshad Khanani hosts a lively and interactive discussion with retina experts, Peter Kaiser, Jeff Heier and Charlie Wykoff about the latest evidence in neovascular age-related macular degeneration (nAMD) and their clinical experience managing these patients.

Although the topic of nAMD management is a serious-minded one, this podcast is inspired by the format of the popular Inside the Actors Studio, hosted for decades by James Lipton, that delivers a Master Class from renowned experts, paired with their responses to fun, quick series questions.

Each expert had the opportunity to sit down with Dr. Khanani and discuss the current state of management of the AMD patient and treatments on the horizon. They also shared some interesting insight into their journeys to becoming vitreoretinal specialists, who has inspired them along the way and fun facts about themselves.

### ***What are the greatest challenges and gaps in clinical care in nAMD management?***

Since its introduction in the early 2000s, anti-vascular endothelial growth factor pharmacotherapy and the use of intravitreal injections has revolutionized the management of a variety of exudative retinal diseases. The exponential increase in anti-VEGF therapy has also led to a threefold increase in clinic visits from a mean of three visits per year to nine.<sup>1</sup> This increased visit frequency related to anti-VEGF agent administration has created service pressures on ophthalmology clinics and also places a significant burden on patients and their caregivers, with barriers to compliance including patient anxiety/discomfort, financial burden, time constraints and lack of transportation.<sup>2</sup> Additionally, increased frequency of intraocular injections also increases the risk of injection-associated adverse events, including endophthalmitis.<sup>3</sup>

“Busy” seems to be the understatement of retinal physicians across the country. Dr. Heier describes his schedule, “Yes, it’s a challenge, I typically see 55-65 patients per day, including study patients in between. That’s 4.5 days per week and a half day in the operating room, which sometimes has cases added into the evening.”

Balancing a full patient load while actively participating in studies can be challenging. Dr. Heier explains, “We’ve looked at different ways to accommodate injections and studies and have found that it seems to be best to incorporate them all together. A busy clinical research site can have to accommodate five to 15 study patients per day, and we intersperse those throughout the day.”

Dr. Kaiser sees around 70 patients each clinic day, half with AMD and a large number requiring injections. He shares a bit of a different perspective to the challenge of a busy clinic and patient complaints of repeated injections. “Yes, we are doing a ton of injections, but the reality is that injections work. When I first started the only option we had was PDT to prevent vision loss, it was depressing. Yes, patients may not like frequent visits and frequent injections, but injections have revolutionized what we do.” Dr. Heier agrees, “I remember when we couldn’t do anything other than focal laser and now, we have patients that are frustrated or upset with visit or treatment frequency. I know that those previous patients who went blind would have been grateful to come in more often.”

### ***What emerging treatments are you most excited about bringing to your AMD patients?***

Therapeutic options for the treatment of AMD are expanding and these novel treatments could potentially be approved for quarterly administration, leading to important improvements in AMD management strategies. These longer acting agents may result in lesser burden to clinicians and patients and also reduce the risk of injection-associated adverse events, while delivering optimum visual outcomes and overall quality of life for patients.

### ***It is a Fun Time to be in Retina. ~Peter Kaiser***

Dr. Khanani asked the experts what they were most excited about when it comes to addressing the patient burden in AMD. Dr. Kaiser responded, “It is a fun time to be in retina. Most of the molecules and delivery systems seem to be working. It has been nice to see 12-week intervals with good efficacy.”

Dr. Wykoff agrees, “we are so fortunate in this field, there is so much that is evolving, but we are still doing same thing we were doing five and 10 years ago. Really, our day to day hasn’t changed.” Dr. Heier adds, “We are in a unique period, we have had anti-VEGF, then a relatively long gap, where we were not really seeing many advances, but I’m feeling like we are on the verge of potentially huge changes, treating patients much less frequently, reducing the burden for patients, families, caregivers, is really important.”

One of the game changers, soon to be added to the nAMD treatment toolbox is Abicipar pegol, a monoDARPin (Designed Ankyrin Repeat Protein - Allergan) that blocks all isoforms of VEGF-A. CEDAR and SEQUOIA were identical global phase 3 studies that assessed the efficacy and safety of Abicipar 8-week and 12-week treatment regimens compared with monthly ranibizumab in treatment-naïve patients with wet AMD. There was a sustained response at 2-years with less frequent dosing of Abicipar compared to standard of care therapy. At week 104 the proportion of patients with stable vision was 93%, 90% and 94% in 8-week Abicipar; 12-week Abicipar and 4-week ranibizumab treatment regimens, respectively, reinforcing the ability of Abicipar to deliver consistent quarterly dosing for the majority of patients. 6 The FDA and EMA are currently reviewing regulatory applications for Abicipar in patients with nAMD with approval anticipated this year.

Brolucizumab is the most recently approved agent in nAMD treatment. Experts share that it is an important advancement for patients that have difficulty coming every 8 weeks, but it is important to have the conversation with patients about the reported increased risk of inflammation. “It is a matter of risk and benefit. Some patients will accept the risk of inflammation, if it means less visits.” Brolucizumab is a humanized single-chain antibody fragment inhibitor of VEGF-A that has a smaller molecular weight (26 kDa) compared to aflibercept (115 kDa) and ranibizumab (48 kDa). Its molecular properties allow a higher molar concentration to be prepared in a 0.05 ml intravitreal injection, which may allow for an extended duration of effect and improved ocular tissue penetration. Phase 3 trials results demonstrated that brolucizumab was non-inferior in BCVA change, compared to aflibercept, and superior reductions in central subfield thickness were achieved with brolucizumab 6mg over aflibercept, while the majority of brolucizumab patients maintained on a quarterly dosing interval after loading until Week 48.<sup>5</sup>

Other treatments under investigation include anti-VEGF agent KSI-301 (Kodiak Sciences) which reported promising data on the safety, efficacy and durability in patients with previously untreated exudative retinal diseases. KSI-301 is an intravitreal agent based on a novel platform, called antibody biopolymer conjugate, or ABC, that uses a large molecular structure to bind to and inhibit vascular endothelial growth factor.

Gene therapy for nAMD, such as RGX-314, an anti-VEGF treatment delivered by gene therapy has the potential to block VEGF for years following a surgical procedure in which a harmless virus, called adeno-associated virus (AAV), carrying the anti-VEGF gene, is injected under the retina in the operating room. In a phase I/II trial with 42 patients, 9 of the 12 patients receiving the highest virus- dose did not require any further anti-VEGF injections in the six months following the RGX-314 injection. No drug-related serious adverse events were observed. “The prospect of a ‘one and done’ is very exciting.” – Peter Kaiser.

Experts agreed that the novel port delivery system (PDS) from Roche/Genentech is very exciting, if it is found to be a safe method of intravitreal anti-VEGF delivery. The LADDER study evaluated durable drug reservoir designed to dispense ranibizumab over time after surgical implantation, with refills performed in the office. Results of Phase 2 study showed that the PDS was well tolerated throughout the mean 22 months study period, even up to 38 months in some patients.

Dr. Kaiser explains, “We need to get efficacy and safety data, and see how it works in real world, really being mindful of the risk/benefit and how a treatment can address a problem in the real world. Getting to 4 months between treatments or a one and done, like with gene therapy, is very exciting.”

Dr. Heier shares, “I’m grateful for the incremental changes we are seeing in treatments, but bigger transformational changes in treatment paradigm is the most exciting to me. Adding value to the patients, achieving better visual acuity with less burden. We need to look at the balance of efficacy and safety for each treatment and tailor to the need of patients.”

Dr. Wykoff agrees, “Its always good to have more tools in the toolbox, the more option to treat patients the better. You don’t know what subset of patients will benefit the most, so I am a big fan of having options, and how they each fit in the treatment paradigm is yet to be determined.”

### ***Key Conversations with Patients***

Clinicians have adopted various treatment regimens, such as treat-and-extend and more personalized as-needed administration, to minimize risk and treatment burden and potentially improve compliance. Several studies have found that real-world outcomes of anti-VEGF therapy are generally worse than those obtained in clinical trials, possibly due to undertreatment.<sup>4</sup> Many have speculated that there are limitations to anti-VEGF therapy, along with the burdensome need for repeated intravitreal injections to sustain efficacy. Despite best efforts, patient adherence to treatment regimens and tempering expectations still requires important conversations.

Dr. Khanani asked how these experts keep their patients committed to their treatment regimen and manage their expectations of treatment.

The experts agreed that patient education is key. Dr. Kaiser spends a lot of time with his treatment naïve patients, “I explain that wet AMD is never cured, and we will treat it for a very long time so it is very important to not skip treatments. I explain how after the first three injections, the loading dose, we may extend, but we are going to treat for a very long time.”

Managing patient expectations against what they learn in the media, or from friends or family can be a sensitive conversation. Dr. Khanani asked the experts how they respond to a patient that comes in for a visit and says that their vision is not improving, and that their neighbor received the same treatment and he is now able to drive. Dr. Kaiser explained his approach, “Be open and honest, everyone is different, even eyes are different, like twins.” He adds, “Patients are smart. They may see highlight of news or some sensationalism of results and ask me, ‘I saw that stem cells made a patient see 20/20, do you really think this is happening?’ so we need to temper excitement, we don’t know how many will work in real life, even though we are having more durable drugs, or some that dry the retina better, but no one has improved visual acuity beyond anti-VEGF. I tell patients that new treatments, combinations, or pathways will hopefully have the same visual acuity results with less injections. I don’t like to over promise with these patients, but do give them some hope.” Dr. Khanani adds that he explains advances in AMD treatment using an example in diabetes, “insulin was a game changer which used to require frequent injections, now insulin is still being used, but there are pumps to alleviate some of the treatment burden.”

Dr. Heier explains how he keeps patients committed to their treatment plans, “It really is one of the biggest challenges. We find we are often negotiating with patients, ‘Can’t it be 7 weeks not 6?’ I always tell them that we know that the closer we are to following regular treatment and monitoring, the greater the chance of getting those results and maintaining results like those we have seen in studies. I remind them about what it was like before these treatments, review real-world data and show them that when they reduce treatment, outcomes fall off.”

### ***Favorite thing a patient can say?***

Treating a patient with nAMD is a longterm relationship, requiring commitment and trust. Although it may be common to hear patient complaints about frequency of visits or time spent in the waiting room, sometimes they can say things that can make or break your day. Our experts were asked to share their favorite and least favorite thing a patient can say.

“Hey doc, you look younger!” Dr. Kaiser jokingly shares as his favorite, but more seriously, it makes his day to hear a patient tell him, “That Fellow, Dr. X, is amazing” because he considers his patients to be like family, “How you treat them really matters to me. You can only teach so much compassion or emotional intelligence, and I’m more interested in compliments about my Fellows than myself.”

Alternatively, the worst thing is when a patient who has been coming in for years, come in without their spouse for the first time, “These are like my family members, the loss affects me.”

Dr. Heier explains that the most rewarding thing he can hear a patient says is how grateful they are for their care. “Especially for those patients anxious about what their vision has become and then they have a dramatic response; hearing how grateful they are is so rewarding.” Alternatively, “The worst thing to hear is when patients who initiate treatment, and they have nice anatomic response, but no visual acuity improvement. This is very frustrating for patients that were hopeful, so I always try to temper initial enthusiasm, tell them that they have an excellent chance at stabilizing and good chance to improve. When their friends can drive again and this patient can’t, it is difficult to keep them committed.”

***If you were not a vitreoretinal surgeon, what do you think you would be?***

Although it is hard to imagine any of our experts not treating retinal disease, but if it were all cured tomorrow, they shared some surprising alternate career paths.

Dr. Kaiser would be applying his keen eye for detail as a professional photographer, adding, “There is really no money in it, but it’s something I really enjoy.”

Dr. Heier explains that if he did not have this career in ophthalmology, “there is no question, I wanted to be a professional tennis player. He adds, in mock seriousness, “but the only thing I was lacking was talent.” Be forewarned if he invites you for a game that Dr. Heier was a high-level tournament player through college.

***Favorite “Retina” word?***

Ophthalmology, and more specifically retina, has some tongue twisters and other terms that are just plain fun to say, (epitheliopathy anyone?) so sticking with the “Inside the Actors Studio” model, our experts were asked to share their favorite retina-related word. Dr. Kaiser’s was, “foveola”, Dr. Heier’s, “drusenoid,” although when it comes to patient care his favorite is, “stability”, as in, “we were able to induce stability in your disease.” Dr. Wykoff didn’t really have a favorite term, but his staff knows that after any surgical intervention he loves to say to a patient, “You have the healthiest eye I will see all day!”

***What do you want your legacy to be?***

Dr. Kaiser’s legacy will be in work he has done and the people he has trained. “The mark I leave will be based on the amazing people I have trained and what they have gone on to do. Teaching is big part of what I do, having residents and Fellows around keeps you on your toes, because you better know the answer. Teaching is like throwing a stone into a pond, I am stone, my ripples can go on to help well beyond Cole Eye Institute, all around the world. When one of my Fellows received a Young Investigator Award, or an Academic appointment it is pretty special.”

Dr. Heier also shares his enjoyment for training Fellows, being a champion for clinical trials and taking the best care of his patients. “I’ve trained excellent Fellows and trained them well. I always try to remain objective and worked really hard to bring new treatments to our profession, without inserting my thoughts and wishes into the process.”

Dr. Wykoff explains, “If my family knows I love them and my patients know that I treated them the way I would treat myself, I have done well.” He adds that his legacy has more to come, and shares his philosophy that, “You can do anything and everything in life, but just not all at the same time.” Looking forward to his next season, Dr. Wykoff plans to apply his expertise to more international projects and outreach.

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## Biographies

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#### Arshad M. Khanani, MD, MA

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Dr. Khanani is a fellowship trained vitreo-retinal specialist and is certified by the American Board of Ophthalmology. As an undergraduate, Dr. Khanani was honored twice with the Howard Hughes Medical Institute Research Award. During his medical training, he received several research awards and designed multiple prospective clinical trials, leading to publications in major ophthalmology journals.

Due to his strong interest in clinical research, Dr. Khanani founded the clinical research section at Sierra Eye Associates. He has been a principal investigator for over 50 clinical trials and has been a top enroller in the country for multiple Phase 1-3 trials. He also serves as a member of clinical trial steering committees and scientific advisory boards for multiple companies. His articles have been published in top ophthalmology journals. Dr. Khanani has also presented his work at major ophthalmology meetings worldwide and has been invited multiple times as a guest speaker nationally and internationally.

Dr. Khanani has received numerous awards of distinction including the Patients' Choice Award, the Compassionate Doctor Recognition Award and the Top 10 Doctor – State Award. He has been named in Marquis Who's Who in the World and has received the Albert Nelson Marquis Lifetime Achievement Award. Dr. Khanani has also received the Honor Award and the Senior Honor Award from the American Society of Retina Specialists for his contributions. He has also been consistently named one of America's Top Ophthalmologists and has also been included in The Leading Physicians of the World publication. In 2019, he received the Nevada Business Magazine "Healthcare Heroes - Physician of the Year" award for his continued dedication to the field of ophthalmology.



## **Peter Kaiser, MD**

Dr. Kaiser graduated magna cum laude with Highest Honors from Harvard College and Harvard Medical School. He completed an ophthalmology residency at the Massachusetts Eye and Ear Infirmary, and a vitreoretinal fellowship at Bascom Palmer Eye Institute before joining the vitreoretinal department of the Cole Eye Institute, Cleveland, Ohio. As a National Institute of Health funded investigator, Dr. Kaiser leads a team involved in the evaluation of vascular biology in age-related macular degeneration and diabetic retinopathy.



Dr. Kaiser is actively involved in clinical research as Study Chairman of numerous major, multi-center, international clinical trials, and principal investigator in dozens of studies for AMD, DR, and other retinal disorders.

He is the founder and director of the Digital Optical Coherence Tomography Reading Center (DOCTR). Complementing his research endeavors, Dr. Kaiser serves on numerous scientific advisory boards and addresses his research interests as an invited speaker at national and international conferences.

Dr. Kaiser is a major contributor to the medical literature having authored 7 textbooks, and more than 250 peer-reviewed papers. He is Editor-in-Chief of Retinal Physician, Associate Editor of International Ophthalmology Clinics, and serves on the editorial boards of Retina, Retina Today, and Ocular Surgery News. Dr. Kaiser has been recognized by the American Academy of Ophthalmology and American Society of Retina Specialists with Senior Achievement Awards and is listed as one of the “Best Doctors in America.” Finally, he is the team ophthalmologist for the Cleveland Cavaliers (National Basketball Association).

## **Jeffrey S. Heier, MD**

Dr. Heier is the Co-President and Medical Director, Director of the Vitreoretinal Service, and Director of Retina Research at Ophthalmic Consultants of Boston (OCB), one of the largest and most prestigious multi-specialty ophthalmology practices in the United States.



Dr. Heier is on the Executive Board of the Retina Society, the Executive Committee of the American Society of Retina Specialists, the President of the New England Ophthalmological Society, and a member of the Macula Society. Dr. Heier is the past Secretary of Online Education for the American Academy of Ophthalmology and the past President of the Center for Eye Research and Education Foundation in Boston, MA.

From the American Academy of Ophthalmology, Dr. Heier received the Senior Achievement Award in 2010, the Secretariat Award in 2007, and the Honor Award in 2003. He is also the recipient of the Honor Award and Senior Honor Award from the American Society of Retina Specialists.

Dr. Heier is one of the leading retinal clinical researchers in the country for new treatments in exudative and non-exudative macular degeneration, diabetic macular edema, venous occlusive disease, vitreoretinal surgical techniques and instrumentation, and diagnostic imaging of the retina. He serves on the Scientific Advisory Board or as Clinical Design Consultant to over thirty biotechnical or pharmaceutical companies. Dr. Heier is the lead investigator on numerous clinical trials, ranging from phase I safety and proof of concept trials to phase IV post-marketing studies.

Dr. Heier lectures nationally and internationally on retinal research and the innovative approach to the treatment of retinal diseases. He has authored or co-authored numerous works in peer-reviewed journals, as well as served as a reviewer for the New England Journal of Medicine, Lancet, Ophthalmology, Archives of Ophthalmology, American Journal of Ophthalmology, Retina, and numerous other journals.

### **Charles C. Wykoff, MD, PhD**

Dr. Wykoff is a board-certified Medical and Surgical Retina Specialist and ophthalmologist with Retina Consultants of Houston. Leading a top international research facility for vitreoretinal diseases, Dr. Wykoff serves as Director of Research at RCH and the Greater Houston Retina Research Foundation (GHRRF). In addition, he serves as the elected Deputy Chair of Ophthalmology for the Blanton Eye Institute, Houston Methodist Hospital. Dr. Wykoff was awarded the American Academy of Ophthalmology Achievement Award in 2015, the American Society of Retina Specialists Honor Award in 2016 and Senior Honor Award in 2018, and was appointed to the OSN Retina 150 in 2016 as an Innovator in Medical and Surgical Retina.



Dr. Wykoff has extensive expertise in clinical trial design and coordination, as well as translational research, publishing over 100 peer-reviewed scientific articles. His research interests pertain to angiogenesis and retinal vascular diseases including age-related macular degeneration, diabetic retinopathy, and venous occlusive diseases, as well as vitreoretinal surgical topics such as retinal tears and retinal detachments, as well as macular surgery for macular holes and macular puckers. He is highly trained and skilled to perform a variety of surgical procedures, and also works with patients to hold off surgery as long as possible with conservative, nonsurgical treatment when possible.

He graduated Phi Beta Kappa from MIT, received his PhD from Oxford University in England while on a Marshall Scholarship, and his medical degree from Harvard Medical School. As a medical student, he co-authored the book *Fighting Global Blindness*. Dr. Wykoff completed his ophthalmology residency and vitreoretinal fellowship at Bascom Palmer Eye Institute, the top-rated eye hospital in the country. While there, he was awarded a Heed Fellowship, the Ronald G. Michels Fellowship Award (the nation's highest)

Dr. Wykoff is an elected member of the Retina Society and the Macula Society, and performs editorial responsibilities including serving as a founding member of the Ophthalmology Retina Editorial Board. Dr. Wykoff holds leadership positions in many scholarly societies including actively serving as the Academic Program Director for the Vit-Buckle Society.