



Published in final edited form as:

Ann Eye Sci. 2022 March ; 7: . doi:10.21037/aes-21-54.

Innovations in the diagnosis and management of uveitis: promising research to address unmet patient needs

Steven Yeh^{1,2}, Ye Huang¹, Joanne Thomas³

¹Truhlsen Eye Institute, University of Nebraska Medical Center, Omaha, NE, USA

²Emory Eye Center, Emory University School of Medicine, Atlanta, GA, USA

³Medical College of Georgia, Augusta, GA, USA.

Uveitis, or inflammation of the uveal tissues (iris, ciliary body and the choroid), and its contiguous structures, can lead to severe visual impairment and is among the leading causes of vision impairment worldwide (1). In clinical practice, specialists in uveitis and ocular immunology are called upon to manage a range of uveitis syndromes—*infectious disease, noninfectious autoimmune conditions, and masquerade syndromes such as lymphoma.* Moreover, ophthalmologists of all subspecialties (i.e., medical and surgical retina, corneal surgeons, orbital/oculoplastic surgeons, and comprehensive ophthalmologists) are called upon to manage uveitis syndromes, emphasizing clear importance to understanding common uveitis syndromes, diagnostic workups, and the state-of-the-art in uveitis and ocular inflammation care.

Recent advances in uveitis disease nomenclature for classification, clinical trials, drug delivery systems, multimodality diagnostic imaging, and laboratory testing involving “omics” technology have provided insight into disease pathogenesis, as well as opportunities for understanding new etiologies of uveitis and therapeutic targets. In this special series of the *Annals of Eye Science* entitled “Innovations in the Diagnosis and Management of Uveitis”, we highlight recent advances in the diagnosis and treatment of uveitis, including both infectious and noninfectious entities, molecular diagnostic techniques, key relationships between gut microbiome and the pathogenesis of uveitis (2). In addition, we also synthesize the literature related to multimodality diagnostic imaging and novel therapies for adults and children with complex inflammatory eye disease. Our recent understanding of uveitis

This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

sye@unmc.edu .

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at <https://aes.amegroups.com/article/view/10.21037/aes-21-54/coif>). The series “Innovations in the Diagnosis and Management of Uveitis” was commissioned by the editorial office without any funding or sponsorship. SY served as the unpaid Guest Editor of the series. The authors have no other conflicts of interest to declare.

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Eye Science* for the series “Innovations in the Diagnosis and Management of Uveitis”. The article did not undergo external peer review.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

associated with checkpoint inhibitor therapy is further discussed, given their increasing use for the benefit for patients with hematologic conditions and cutaneous malignancy, as well as their potential insight into uveitis pathology (3).

In consideration of these key areas of discovery and growth of the field of uveitis, we highlight subject matter for clinicians and clinician-investigators interested in ongoing ophthalmic research, which will address unmet patient care needs.

Diagnostic imaging in uveitis

In clinical practice, diagnostic imaging continues to play a continued role in defining the local of disease pathologies, particularly subclinical disease. While optical coherence tomography (OCT) is a mainstay of detecting and monitoring macular edema due to noninfectious uveitis, the leading cause of vision impairment in uveitis, multimodality imaging can be extremely helpful for the detection of posterior segment disease [e.g., indocyanine green angiography (ICGA) in birdshot retinochoroidopathy] and following disease activity in other posterior segment conditions (e.g., fundus autofluorescence for serpiginous choroidopathy).

Zheng and Sharma describe an array of imaging modalities used in the clinic and the laboratory for the objective assessment of anterior uveitis, intermediate uveitis and scleritis (4). Established guidance for the assessment of uveitis most commonly employs Standardization of Uveitis Nomenclature criteria for the assessment of anterior chamber (AC) cell, AC flare, and vitreous haze (5). Yet, recent work by Zheng and Sharma (4) has demonstrated strong correlation between AC inflammation and volumetric analysis of AC inflammation using anterior segment OCT (AS-OCT). Swept-source AS-OCT is currently under investigation for the assessment of AC flare in addition to cell and may provide another modality for objective measures for uveitis patients during clinical follow-up, as well as for research purposes.

Another unique application of AS-OCT discussed by Zheng and Sharma involves its use for scleritis and episcleritis. Findings identified in scleritis patients by AS-OCT include nodular densities, deep hyporeflective cavities that correspond to dilated vessels, which show interval resolution with anti-inflammatory therapy. Through continued work in these areas, it is likely that these objective measures would also be applicable to broader use in the future, particularly with a growing body of evidence correlating clinically active episcleritis and scleritis with AS-OCT and over longitudinal follow-up.

Vogt-Koyanagi-Harada syndrome (VKH) and uveitis associated with checkpoint inhibitors: balancing autoimmunity and tumor immunity in the context of melanocytic antigen targeting

Prior elegant studies have reported the pathogenesis of VKH, namely T-cell targeting of melanocyte antigen including MART-1 and gp100 antigens in patients with VKH and sympathetic ophthalmia, which bears similarities in T-cell targeting (6). These interplay between T-cells and melanocytic antigen has also been observed in melanoma

immunotherapy, in which disruption of T-cell regulation leads to immune-related adverse events (irAEs) including uveitis, papillitis, vitiligo, and poliosis in addition to other documented irAEs (7–9). Timely reviews related to VKH and checkpoint inhibitor uveitis highlight the parallels between these topics (3,10).

VKH

VKH is a rare but severe autoimmune disease presenting as a bilateral granulomatous panuveitis. The pathogenesis involves CD4⁺ T-cells that attack melanocytes in various organ systems, which can also lead to extraocular complications such as meningismus, vitiligo, and poliosis. Our understanding of the clinical manifestations and proper treatment for this disease has continued to evolve over the years. O’Keefe summarizes recent advancements in the diagnosis and treatment of VKH (10).

Specifically, there are a number of well-studied findings on OCT that are diagnostically predictive of VKH including retinal detachment, subretinal hyperreflective dots, subretinal membranous structures, and retinal pigment epithelium (RPE) folds (11,12). Optical coherence tomography angiography (OCTA) has emerged as a new technique that could potentially serve as an alternative to ICGA in VKH diagnosis (13). It was found to successfully differentiate between patients with VKH and those with central serous chorioretinopathy (CSR). The main limitation of OCTA’s utility is its smaller field of view than fluorescein angiography at this time. Enhanced depth imaging (EDI) OCT is another imaging technique that has also demonstrated utility in differentiating choroidal granulomas of VKH from those seen in other inflammatory uveitis such as sarcoidosis and tuberculosis (14). As such, the application of OCTA and EDI-OCT in VKH diagnosis remains a promising area to be studied.

While systemic corticosteroids remain the mainstay of VKH treatment, recent studies have revealed possible alternative or adjunctive forms of treatment. In patients without systemic signs, subtenon triamcinolone injections may be used as a primary treatment for VKH, although their long-term use and application require further investigation (15). Paredes *et al.* observed improved visual outcomes when comparing prompt initiation of immunomodulatory therapy (IMT) when compared to steroid monotherapy or delayed IMT initiation (16). Urzua *et al.* noted that a subset of patients with corticosteroid-refractory disease could benefit the most from early IMT initiation (17). Additional research is needed on the benefit of prompt IMT therapy. Biological response modifiers (BRMs), such as adalimumab, rituximab, and infliximab, have also demonstrated utility in treating VKH refractory to conventional immunosuppression (18–26). Of note, VKH is understood to be primarily T-cell mediated, but rituximab, a monoclonal antibody that targets CD20, has been observed to show promising efficacy signals as well, underscoring the need to understand the role of B-cells in VKH and potential targeting by BRMs.

Uveitis associated with checkpoint inhibitor therapy

The use of immune checkpoint inhibitors and targeted therapy in cancer treatment has become increasingly widespread. These drugs have targets such as CTLA-4 (ipilimumab), PD-1 (pembrolizumab, nivolumab), and PD-L1 (atezolizumab, avelumab, durvalumab). By

binding to these receptors or ligands, these drugs can stimulate T-cell activity, subsequently enhancing the detection and destruction of malignant cells (7,27). Targeted therapy drugs work to curb mutations leading to uncontrolled proliferation of cancer cells, including those that affect the mitogen-activated protein kinase pathway (trametinib) and BRAF enzyme (dabrafenib, vemurafenib) (28–30). They have proven efficacy in treatment of metastatic melanoma, squamous cell carcinoma, and non-small cell lung cancer, to name a few. However, they have also been found to cause ocular complications on rare occasions. These include cases of uveitis, ranging from isolated anterior uveitis to panuveitis, and occasionally VKH-like syndromes with systemic symptoms. While these are scarcely observed compared to more common side effects such as fatigue and skin rash, the consequences can be devastating (27). Arepalli and Venkat delineate the documented adverse effects from these drugs in their review (3,7).

Although rare, these instances represent additional challenges towards the patient's cancer treatment. The Common Terminology Criteria for Adverse Events (CTCAE) recommends that for ocular irAEs categorized as a grade 3 or 4 uveitis, cancer therapy should be withheld entirely (31). However, multiple documented cases have been successfully treated with local steroid therapy alone without requiring cancer therapy cessation or initiation of systemic corticosteroids (7). Nevertheless, these decisions should be made on a case-by-case basis with oncology to determine what is the optimal treatment choice for the patient. In instances of systemic irAEs, abrupt discontinuation of cancer therapy and systemic steroids may be necessary. Further research is necessary to explain the mechanism behind these adverse effects as well as the appropriate treatment.

Uveitis and the intestinal microbiota: potential therapeutic benefit from a gut check

While the majority of medications for noninfectious uveitis have included systemic and local corticosteroid, as well as steroid sparing disease modifying anti-rheumatic drugs (DMARDs) or BRMs, there has been growing interest in the scientific community involved in the study of autoimmunity focusing on non-pharmacologic measures include the role of diet and stress in preventing or treating inflammatory eye conditions.

Gut microorganisms previously thought to be commensal bacteria, viruses, and fungi (i.e., commonly thought to be passive bystanders) actively contribute to mucosal and systemic homeostasis. Pathologic disruption of this homeostasis, termed intestinal dysbiosis, has been associated with autoimmune diseases including ankylosing spondylitis, multiple sclerosis, and rheumatoid arthritis and is currently the subject of rigorous investigation by Lin *et al.*, summarized in their recent review in this special series of the *Annals of Eye Science* (2).

Their recent investigation has shown that diets rich in fermentable fibers give rise to increased intestinal bacterial production of short chain fatty acids, which may be protective against uveitis through an increase in regulatory T-cells and decreased intestinal permeability, which is illustrated in their article. Further understanding of bacterial promotion of potentially key mediators in immune regulation may open up therapeutic

opportunities through antibiotic regimens, probiotics and supplementation of bacterial metabolites, and studies in this area are ongoing.

Assessing pediatric uveitis patients and targeting therapy

With additional systemic immunomodulatory BRM therapies and local therapies on the horizon, our field's ability to effectively treat intraocular inflammation and macular edema, leading to visual acuity improvement, has continued to improve and evolve. Yet, patient reported outcomes measures remain central to our understanding of how therapies precisely impact individuals and improve quality-of-life. These challenges are particularly notable in pediatric uveitis, notably juvenile idiopathic arthritis (JIA), where the impact of vision disability, chronic disease, and medication use can be a lifelong journey that requires long-term care with a holistic approach to the patient, family and the patient's support network.

Most pediatric uveitis cases are due to a non-infectious etiology, and JIA is the most common systemic association. While pediatric uveitis only accounts for 5–10% of all uveitis cases, it poses unique diagnostic and therapeutic challenges (32). Asymptomatic presentation can lead to delayed diagnosis with an increased disease burden into adulthood. The review by McDonald *et al.* analyzed the current methods for understanding outcomes in pediatric uveitis patients (33). Previously, ophthalmic examination and general quality of life (QOL) measures have been utilized. While ophthalmic exam does evaluate for important visual outcomes, it does not take into consideration QOL measures. On the other hand, general health QOL questionnaires may not fully assess the visual impact of uveitis. Even the emergence of health-related QOL measures in children such as the Pediatric Quality of Life Inventory (PedsQL), Child Health Questionnaire (CHQ) and Childhood Health Assessment Questionnaire (CHAQ) has not fully assessed health outcomes in terms of impact on vision health and treatment.

Vision-related QOL (VR-QOL) questionnaires have emerged to meet this need. The National Eye Institute Visual Function Questionnaire (NEI VFQ-25) includes domains of vision health, social functioning, and mental health (34). While this has validity and reliability in adult patients, the NEI VFQ-25 is not a valid measure in children. Other VR-QOL measures for children have also been developed including the Cardiff Visual Ability Questionnaire for Children (CVAQC), Impact of Vision Impairment on Children (IVI_C) and the Vision-related Quality of Life of Children and Young People (VQoL_CYP). While these focus on both vision and QOL measures in children, they do not include uveitis related ocular complications and do not fully capture the outcomes of pediatric uveitis.

With a need for a pediatric uveitis specific VR-QOL questionnaire, Angeles-Han *et al.* developed the Effect of Youngsters' Eyesight on Quality of Life (EYE-Q). This has validity and reliability as demonstrated by several single center cohort studies for use in patients aged 5–18. EYE-Q more sensitively assesses visual function and better appreciates the burden of treatment compared to the general pediatric VR-QOL measures (35,36). As the EYE-Q contains school-specific items, it has not been validated for children below the age of 5. Currently, no questionnaire exists for a uveitis specific QOL measure in non-school age children, and this remains a vital area for further research.

As pediatric uveitis is sight-threatening, treatment may be challenging yet critical for vision preservation and long-term function, schooling, and activities of daily living. Children may be more vulnerable to the side effects of mainstay therapies commonly utilized for adult uveitis patients. Long-term corticosteroid therapy for pediatric uveitis can lead to increased ocular hypertension and the development of cataracts in children compared to their adult counterparts (37). Because of this, DMARDs and biologics are important therapies to consider in pediatric uveitis. A review by Thomas *et al.* outlined the efficacy of biologics for pediatric uveitis (38). Tumor necrosis factor α (TNF- α) inhibitors such as adalimumab have been shown to decrease risk of treatment failure compared to methotrexate alone (39). In pediatric uveitis, tocilizumab, an interleukin 6 (IL-6) inhibitor, showed improvement of disease and the allowance of corticosteroid drop tapering in patients who were refractory to both TNF- α inhibitors and DMARDs (40).

While options for biologic therapies for pediatric uveitis are available, some patients are unable to attain remission. JAK inhibitors are the emerging class of biologics for treatment for these individuals. Evidence of the efficacy of JAK inhibitors is limited, but case studies have shown improvement of uveitis in patients refractory to other therapies (41,42). In addition, JAK-inhibitors did not show systemic side effects in the 7-month follow-up period. Further investigation of the role of JAK inhibition for treatment is needed, and currently a clinical trial studying the efficacy of baricitinib, a JAK inhibitor, in pediatric patients with juvenile idiopathic arthritis-uveitis (JIA-U) is ongoing (43).

Summary

In summary, the field of uveitis remains promising with advances in diagnostic imaging and further understanding of disease pathogenesis. While research related to diet and microbiome are performed through extensive research in the laboratory and through clinical translational work, understanding our colleagues' work in cutaneous oncology, namely melanoma, can also provide insight into diseases such as VKH. With these promising therapeutics being developed, improving our objective metrics of inflammation should be paralleled by patient-reported outcomes measures such that we can measure our impact and refine our ability to relate to patients' individual and collective experience. Beyond infectious and noninfectious uveitis, research is also needed for uveitis masquerade syndromes, including promising targeted and adjuvant therapies. We hope this special edition of *Annals of Eye Science* will provide the reader with broad insight on the "State-of-the-art" in uveitis and future directions to care for this complex array of ocular inflammatory diseases.

Funding:

This project was supported by the National Eye Institute/National Institutes of Health core grant P30-EY06360 (Department of Ophthalmology, Emory University School of Medicine), National Eye Institute of the National Institutes of Health under award number R01 EY029594 (S Yeh). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. This research was also supported an unrestricted departmental grant from Research to Prevent Blindness, Inc. to the Emory Eye Center, Emory University School of Medicine. Funding support was also provided by the Macula Society Retina Research Foundation, the Association for Research in Vision and Ophthalmology and the Stanley M. Truhlsen Family Foundation.

References

1. Nussenblatt RB. The natural history of uveitis. *Int Ophthalmol* 1990;14:303–8. [PubMed: 2249907]
2. Lin P Altering the intestinal microbiota for therapeutic benefit in uveitis. *Ann Eye Sci* 2020;5:26.
3. Arepalli S, Venkat AG. Uveitis secondary to cancer therapeutics. *Ann Eye Sci* 2020;5:19.
4. Zheng A, Sharma S. Zhengons in anterior uveitis, intermediate uveitis, and scleritis. *Ann Eye Sci* 2020;5:23.
5. Jabs DA, Nussenblatt RB, Rosenbaum JT, et al. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol* 2005;140:509–16. [PubMed: 16196117]
6. Sugita S, Sagawa K, Mochizuki M, et al. Melanocyte lysis by cytotoxic T lymphocytes recognizing the MART-1 melanoma antigen in HLA-A2 patients with Vogt-Koyanagi-Harada disease. *Int Immunol* 1996;8:799–803. [PubMed: 8671669]
7. Venkat AG, Arepalli S, Sharma S, et al. Local therapy for cancer therapy-associated uveitis: a case series and review of the literature. *Br J Ophthalmol* 2020;104:703–11. [PubMed: 31409649]
8. Yeh S, Karne NK, Kerkar SP, et al. Ocular and systemic autoimmunity after successful tumor-infiltrating lymphocyte immunotherapy for recurrent, metastatic melanoma. *Ophthalmology* 2009;116:981–989.e1. [PubMed: 19410956]
9. Crosson JN, Laird PW, Debiec M, et al. Vogt-Koyanagi-Harada-like syndrome after CTLA-4 inhibition with ipilimumab for metastatic melanoma. *J Immunother* 2015;38:80–4. [PubMed: 25658618]
10. O'Keefe GAD. Update on the diagnosis and treatment of Vogt-Koyanagi-Harada syndrome. *Ann Eye Sci* 2020;5:22.
11. da Silva FT, Sakata VM, Nakashima A, et al. Enhanced depth imaging optical coherence tomography in long-standing Vogt-Koyanagi-Harada disease. *Br J Ophthalmol* 2013;97:70–4. [PubMed: 23099292]
12. Liu XY, Peng XY, Wang S, et al. Features of optical coherence tomography for the diagnosis of Vogt-Koyanagi-Harada disease. *Retina* 2016;36:2116–23. [PubMed: 27145255]
13. Aggarwal K, Agarwal A, Deokar A, et al. Distinguishing features of acute Vogt-Koyanagi-Harada disease and acute central serous chorioretinopathy on optical coherence tomography angiography and en face optical coherence tomography imaging. *J Ophthalmic Inflamm Infect* 2017;7:3. [PubMed: 28091938]
14. Invernizzi A, Mapelli C, Viola F, et al. Choroidal granulomas visualized by enhanced depth imaging optical coherence tomography. *Retina* 2015;35:525–31. [PubMed: 25105317]
15. Hosoda Y, Hayashi H, Kuriyama S. Posterior subtenon triamcinolone acetate injection as a primary treatment in eyes with acute Vogt-Koyanagi-Harada disease. *Br J Ophthalmol* 2015;99:1211–4. [PubMed: 25792626]
16. Paredes I, Ahmed M, Foster CS. Immunomodulatory therapy for Vogt-Koyanagi-Harada patients as first-line therapy. *Ocul Immunol Inflamm* 2006;14:87–90. [PubMed: 16597537]
17. Urzua CA, Velasquez V, Sabat P, et al. Earlier immunomodulatory treatment is associated with better visual outcomes in a subset of patients with Vogt-Koyanagi-Harada disease. *Acta Ophthalmol* 2015;93:e475–80. [PubMed: 25565265]
18. Caso F, Rigante D, Vitale A, et al. Long-lasting uveitis remission and hearing loss recovery after rituximab in Vogt-Koyanagi-Harada disease. *Clin Rheumatol* 2015;34:1817–20. [PubMed: 25224382]
19. Couto C, Schlaen A, Frick M, et al. Adalimumab Treatment in Patients with Vogt-Koyanagi-Harada Disease. *Ocul Immunol Inflamm* 2018;26:485–9. [PubMed: 27775450]
20. Jeroudi A, Angeles-Han ST, Yeh S. Efficacy of adalimumab for pediatric Vogt-Koyanagi-Harada syndrome. *Ophthalmic Surg Lasers Imaging Retina* 2014;45:332–4. [PubMed: 25037015]
21. Khalifa YM, Bailony MR, Acharya NR. Treatment of pediatric vogt-koyanagi-harada syndrome with infliximab. *Ocul Immunol Inflamm* 2010;18:218–22. [PubMed: 20482402]
22. Niccoli L, Nannini C, Cassarà E, et al. Efficacy of infliximab therapy in two patients with refractory Vogt-Koyanagi-Harada disease. *Br J Ophthalmol* 2009;93:1553–4. [PubMed: 19854741]

23. Su E, Oza VS, Latkany P. A case of recalcitrant pediatric Vogt-Koyanagi-Harada disease successfully controlled with adalimumab. *J Formos Med Assoc* 2019;118:945–50. [PubMed: 30616991]
24. Takayama K, Obata H, Takeuchi M. Efficacy of Adalimumab for Chronic Vogt-Koyanagi-Harada Disease Refractory to Conventional Corticosteroids and Immunosuppressive Therapy and Complicated by Central Serous Chorioretinopathy. *Ocul Immunol Inflamm* 2020;28:509–12. [PubMed: 31268769]
25. Umrans RMR, Shukur ZYH. Rituximab for sight-threatening refractory pediatric Vogt-Koyanagi-Harada disease. *Mod Rheumatol* 2018;28:197–9. [PubMed: 26154298]
26. Wang Y, Gaudio PA. Infliximab therapy for 2 patients with Vogt-Koyanagi-Harada syndrome. *Ocul Immunol Inflamm* 2008;16:167–71. [PubMed: 18716952]
27. Dalvin LA, Shields CL, Orloff M, et al. Checkpoint inhibitor immune therapy: Systemic Indications and Ophthalmic Side Effects. *Retina* 2018;38:1063–78. [PubMed: 29689030]
28. Choe CH, McArthur GA, Caro I, et al. Ocular toxicity in BRAF mutant cutaneous melanoma patients treated with vemurafenib. *Am J Ophthalmol* 2014;158:831–837.e2. [PubMed: 25036880]
29. Moorthy RS, Moorthy MS, Cunningham ET Jr. Drug-induced uveitis. *Curr Opin Ophthalmol* 2018;29:588–603. [PubMed: 30222658]
30. Welsh SJ, Corrie PG. Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. *Ther Adv Med Oncol* 2015;7:122–36. [PubMed: 25755684]
31. Common Terminology Criteria for Adverse Events version 5.0. November 27, 2017. Available online: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
32. Edelsten C, Reddy MA, Stanford MR, et al. Visual loss associated with pediatric uveitis in english primary and referral centers. *Am J Ophthalmol* 2003;135:676–80. [PubMed: 12719076]
33. McDonald JM, Yeh S, Angeles-Han ST. Pediatric uveitis: EYE-Q and metrics beyond visual acuity. *Ann Eye Sci* 2020;5:20.
34. Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol* 2001;119:1050–8. [PubMed: 11448327]
35. Angeles-Han ST, Yeh S, McCracken C, et al. Using the Effects of Youngsters' Eyesight on Quality of Life Questionnaire to Measure Visual Outcomes in Children With Uveitis. *Arthritis Care Res (Hoboken)* 2015;67:1513–20. [PubMed: 26037544]
36. McDonald J, Utz V, Hennard T, et al. AB1019 The effect of treatment regimen on health-related quality of life and functioning in children with uveitis. *Ann Rheum Dis* 2019;78:1975.
37. Cunningham ET Jr. Uveitis in children. *Ocul Immunol Inflamm* 2000;8:251–61. [PubMed: 11262655]
38. Thomas J, Kuthyar S, Shantha JG, et al. Update on biologic therapies for juvenile idiopathic arthritis-associated uveitis. *Ann Eye Sci* 2021;6:19. [PubMed: 34131629]
39. Ramanan AV, Dick AD, Benton D, et al. A randomised controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE Trial). *Trials* 2014;15:14. [PubMed: 24405833]
40. Ramanan AV, Dick AD, Guly C, et al. Tocilizumab in patients with anti-TNF refractory juvenile idiopathic arthritis-associated uveitis (APTITUDE): a multicentre, single-arm, phase 2 trial. *Lancet Rheumatol* 2020;2:e135–41. [PubMed: 32280950]
41. Bauermann P, Heiligenhaus A, Heinz C. Effect of Janus Kinase Inhibitor Treatment on Anterior Uveitis and Associated Macular Edema in an Adult Patient with Juvenile Idiopathic Arthritis. *Ocul Immunol Inflamm* 2019;27:1232–4. [PubMed: 31268748]
42. Miserocchi E, Giuffrè C, Cornalba M, et al. JAK inhibitors in refractory juvenile idiopathic arthritis-associated uveitis. *Clin Rheumatol* 2020;39:847–51. [PubMed: 31897953]
43. A Study of Baricitinib (LYIn Participants From 2 Years to Less Than 18 Years Old with Active JIA-Associated Uveitis or Chronic Anterior Antinuclear Antibody-Positive Uveitis. Available online: <https://ClinicalTrialsgov/show/NCT04088409>