



Published in final edited form as:

*Am J Ophthalmol.* 2012 September ; 154(3): 429–435.e2. doi:10.1016/j.ajo.2012.05.011.

## Uveitis, the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), and Intravitreal Biologics for Ocular Inflammation Short title: Uveitis, CATT, and intravitreal biologics

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### Abstract

**Purpose**—To provide perspective on the implications of the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) on intravitreal biologic agents in uveitis and retinal diseases in which ocular inflammatory pathways are central to their pathogenesis

**Design**—Interpretative essay

**Methods**—Literature review and interpretation

**Results**—Besides the clear importance of CATT from a patient treatment perspective in age-related macular degeneration (AMD), these data highlight the critical relevance of highly specific protein immunotherapies offered with biologic agents. The CATT trial also provides a reminder regarding the importance of rigorous efficacy and safety monitoring required when administering intravitreal biologic therapy. Within the field of uveitis, systemic and local biologics have been utilized to effectively treat uveitis, targeting pathways implicated in both angiogenesis and inflammation (e.g. tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ] and interleukin-2 pathways), and research on intravitreal biologic therapy for uveitis and AMD will continue to expand. With over 25 ongoing clinical trials on intravitreal biologic therapy for AMD, enthusiasm for vanguard biologic therapies should be tempered by judicious monitoring for adverse events.

**Conclusion**—The importance of the CATT trial encompasses day-to-day treatment decisions for AMD, as well as lessons on how biologics for ocular disease should be implemented into clinical practice. Specifically, the introduction of intravitreal biologic therapies into clinical practice for

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*Statement about conformity:* Because of the interpretive nature of this perspectives article, IRB approval was not sought during the preparation of this manuscript.

*Financial Disclosures:* Dr. Nussenblatt – None; Dr. Yeh – None; Dr. Albini – Grant support (Genentech), Dr. Moshfeghi – Grant support (Palm Beach Community Trust Fund, Palm Beach, FL)

*Contributions of authors:* Individual author contributions are as follows – Conception and design (SY, TAA, RBN), analysis and interpretation (SY, TAA, AAM, RBN), writing the article (SY, TAA, RBN), critical revision (SY, TAA, AAM, RBN), final approval (SY, TAA, AAM, RBN), data collection (SY), provision of patient materials (not applicable), statistical expertise (not applicable), obtaining funding (SY, RBN), literature search (SY, TAA, AAM, RBN), administrative or technical support (SY, TAA, AAM, RBN)

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uveitis, AMD, and other ocular diseases in which inflammation is involved, should be guided by a clear understanding of the immunotherapeutic agent and its molecular target and with rigorous monitoring for both patient benefit and patient safety.

In the multicenter, randomized, Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) study, the comparative efficacy of the two biologic agents ranibizumab (Lucentis, Genentech) and bevacizumab (Avastin, Genentech) was evaluated in a prospective and controlled fashion.<sup>1</sup> The CATT study showed that both monoclonal antibodies targeting vascular endothelial growth factor (VEGF), despite differences in binding affinity, molecular structure, and FDA-approved labels<sup>2</sup>, compared favorably in their ability to improve and stabilize vision at the one-year time point.<sup>1</sup> The mechanisms underlying age-related macular degeneration (AMD) are incompletely understood, and likely involve angiogenic, inflammatory, and structural wound healing pathways.<sup>3</sup> The CATT trial illustrates the tremendous impact of specific immunologic targeting of these molecular pathways for retinal disease and answers critical questions in the day-to-day management of AMD. Moreover, the manner in which the trial was conducted provides insight and guidance for future research in another entire category of disease processes – uveitis and ocular immunologic diseases – in which biologic therapies are a mainstay of immunosuppressive therapy. Herein, we discuss the implications of the CATT trial to uveitis, the lessons learned from prior administration of intravitreal biologics, and considerations regarding the manner in which novel intravitreal biologic therapies for uveitis and retinal diseases should be introduced into clinical practice.

## **Molecular targeting in age-related macular degeneration: Vascular endothelial growth factor and beyond**

VEGF is a secreted glycoprotein involved in promoting vascular permeability and angiogenesis and plays a role in mediating tumor angiogenesis, inflammatory conditions including rheumatoid arthritis, psoriasis, and ocular neovascularization.<sup>4</sup> The clinical efficacy of VEGF inhibition with ranibizumab was initially demonstrated in prospective controlled trials for AMD<sup>5-7</sup> with subsequent trials for retinal vein occlusions and diabetic retinopathy. Bevacizumab also demonstrated efficacy following its initial systemic intravenous administration for AMD<sup>8</sup>, and then subsequently via intravitreal delivery to patients with AMD.<sup>9-12</sup> It is notable that despite differences in molecular structure, binding affinity, and biological half-life, bevacizumab was not inferior to ranibizumab in the majority of treatment arms in the CATT study at one-year.<sup>1</sup>

Ranibizumab is a 48 kDa humanized, monoclonal antibody fragment (Fab), which binds to multiple isoforms of VEGF, and has a terminal biological half-life is approximately 3 days.<sup>13</sup> Bevacizumab, a 149 kDa humanized, full-length monoclonal IgG antibody, is derived from the same murine monoclonal antibody hybridoma as ranibizumab, but has a longer half-life of 9.8 days in human eyes.<sup>14</sup> In addition, because ranibizumab was engineered through the process of *in vitro* affinity maturation, the affinity improvement of ranibizumab relative to Fab-12 (i.e. the Fab fragment of bevacizumab) approaches 100-fold. Moreover, the better retinal tissue penetration of ranibizumab when compared to trastuzumab (Herceptin, Genentech), a full-length 150 kDa monoclonal antibody bearing structural framework similarities to bevacizumab, favored ranibizumab as the preferred therapeutic choice for AMD.<sup>15</sup> With the CATT study results demonstrating comparable efficacy between the two medications and no obvious adverse safety signals with bevacizumab, both medications offer effective therapeutic alternatives to consider for both AMD and other off-labels indications including uveitis and other retinal diseases.

Besides biologics inhibiting VEGF in AMD, other molecular pathways relevant to AMD pathogenesis, which may provide rational therapeutic targets, include those involving lipofuscin accumulation, oxidative damage, and chronic inflammation (both complement- and non-complement-mediated).<sup>16–18</sup> Several biologic therapies relevant to these pathways have been administered previously for uveitis and AMD both systemically<sup>19, 20</sup> and via intravitreal route<sup>21, 22</sup> and their efficacy and safety warrant discussion.

## **Intravitreal biologics for uveitis: anti-vascular endothelial growth factor agents and others**

While data reporting the efficacy of systemic biologics targeting diffusible cytokines, chemokines, and cell surface receptors for uveitis have been reported frequently in the setting of prospective trials<sup>23, 24</sup> and retrospective series<sup>25, 26</sup>, intravitreal biologic therapy for uveitis is a relatively recent phenomenon with growing enthusiasm particularly following the successful use of bevacizumab and ranibizumab. Limited studies have reported the intravitreal off-label use bevacizumab, ranibizumab, infliximab, and rituximab for uveitis and related conditions (e.g. vitreoretinal lymphoma).

Specifically, bevacizumab and ranibizumab have been used to treat and stabilize secondary complications of uveitis, which include uveitic macular edema<sup>27</sup>, choroidal neovascularization<sup>28</sup>, and retinal vasculitis<sup>29</sup> although their use for primary suppression of inflammation has not been established. More recent studies have suggested that a combination of systemic immunosuppression and local anti-VEGF modulation are beneficial for choroidal neovascularization secondary to inflammation-driven processes such as punctate inner choroidopathy and multifocal choroiditis.<sup>28</sup> These data suggest that although anti-VEGF therapies are effective for these conditions, likely owing to their anti-vasopermeability properties, the complex proteomic milieu of uveitis requires further study to identify appropriate immunologic targets for anti-inflammatory therapy. The use of combination therapy targeting angiogenesis and other pathogenic pathways may be preferred for both AMD and uveitis.<sup>18</sup>

Amongst systemically administered biologics for uveitis, the anti-tumor necrosis factor-alpha (TNF-alpha) antagonists (e.g. infliximab, adalimumab, etanercept) have received considerable attention, showing efficacy for juvenile idiopathic arthritis (JIA), HLA-B27-associated conditions, and Behcet's disease.<sup>23, 24, 30</sup> The efficacy of daclizumab, a humanized anti-interleukin-2 receptor (IL-2 receptor) has also been described for birdshot retinochoroidopathy, sarcoidosis, and Vogt-Koyanagi-Harada syndrome.<sup>31, 32</sup> Other biologics with reported efficacy for uveitis including alemtuzumab (anti-CD52 monoclonal antibody)<sup>33</sup> and anakinra (anti-IL-1R).<sup>34</sup> However, systemic side effects may be prohibitive for some of these medications, and the long-term side effect profile is unknown, although retrospective data suggest no increased mortality or cancer risk associated with the anti-TNF-alpha family of medications.<sup>35</sup>

Because of systemic side effects associated with each of these medications, local immunomodulation is a desirable approach; however, it is not clear whether local, transient immunomodulation of soluble factors will prevent the recurrence of inflammation since the mechanisms underlying uveitis are thought to involve systemic T-cell targeting of self-antigen in patients with a genetic predisposition.<sup>36, 37</sup>

## **Lessons from intravitreal infliximab**

The intravitreal delivery of infliximab for AMD, uveitis and diabetic macular edema was met with considerable interest initially, and early results suggested its possible role in

decreasing choroidal neovascularization and treating cystoid macular edema, which is also the most common cause of visual morbidity in uveitis. However, early reports were uncontrolled nonrandomized case series with variable outcomes and limited follow-up.<sup>22, 38</sup> More recent prospective studies evaluating the safety and efficacy of infliximab for diabetic macular edema and AMD were subsequently conducted.<sup>39–41</sup> However, several concerning reports described electroretinographic abnormalities in patients treated with intravitreal infliximab<sup>39</sup> in addition to severe panuveitis requiring posterior vitrectomy.<sup>21, 39, 40</sup> These adverse events, combined with modest efficacy for the long-term control of uveitis reduced the initial enthusiasm regarding its intravitreal use outside the confines of a controlled, clinical trial.<sup>42</sup>

## Lessons from intravitreal rituximab

One example of the efficacy of intravitreal therapies with highly specific targeting is the use of rituximab, a chimeric monoclonal antibody targeting CD20, which is a cell surface marker for the uveitis masquerade syndrome B-cell lymphoma. Rituximab, originally marketed for systemic non-Hodgkin's lymphoma (NHL), has now been FDA-approved for NHL, rheumatoid arthritis, Wegener's granulomatosis and microscopic polyangiitis. Rabbits given rituximab via intravitreal delivery prior to its use in patients demonstrated no significant clinical or histologic signs of inflammation although mild vitritis was observed in one report.<sup>43, 44</sup> Based on this encouraging data, intravitreal rituximab was administered and was found to effectively eradicate primary vitreoretinal lymphoma (PVRL). Although the reports of its efficacy are encouraging,<sup>44, 45</sup> further evaluation of the efficacy and safety of rituximab for intraocular lymphoma in the context of a prospective clinical trial is needed. Moreover, because 15% of patients with central nervous system (CNS) lymphoma develop PVRL and 65–90% of patients with PVRL eventually develop CNS lymphoma, the cooperative efforts of ophthalmologist and oncologist are necessary, as intravitreal chemotherapy may serve as an adjuvant to systemic chemotherapy or radiation.<sup>46</sup>

## Future intravitreal biologic considerations

Within the study of uveitis and ocular inflammation, the inflammatory milieu continues to be unraveled, providing numerous cytokines, chemokines and cell surface markers of immune cell activation and targets for therapy and biologics provide attractive potential to specifically affect these targets. This group of medications is particularly relevant for patients who are unable to tolerate systemic medications or are unable to have local corticosteroid due to risk of glaucomatous optic neuropathy progression or cataract development. Specifically, the local delivery of biologic agents may minimize the side effects of systemic biologics while concomitantly limiting the cataractogenic and ocular hypertensive risk of periocular and intravitreal corticosteroids. In addition, the further identification of biomarkers within patient serum may help to dictate which patients will respond to specific biologic therapies. Given that uveitis represents a heterogeneous group of ocular inflammatory conditions, it is likely that certain biologics may work better for specific phenotypes.

Recent research on aqueous humor cytokine profiling in patients with AMD and serum and ocular fluid biomarkers in AMD subtypes also highlight the burgeoning interest in biologic therapies for AMD. According to the National Clinical Trials database, there are over 25 trials for AMD in which biologics are being or have been tested for AMD with safety monitoring requisite prior to the introduction of any new therapeutic. These biologics target integrins, complement and other inflammatory pathways relevant to both wet and dry AMD and are summarized in the Table. Conducting trials in this prospective manner will help us to adequately assess and safely delivery these medications for wet and dry AMD.

Given the established inflammatory pathways of uveitis, biologic therapies provide an attractive potential to specifically affect these targets. While bevacizumab, ranibizumab and infliximab have been used for both indications, other parallels exist, although there are far fewer prospective clinical trials evaluating intravitreal biologics for uveitis. Although uveitis is the third leading cause of visual blindness in developing countries, it remains a relatively small market compared to other retinal conditions including AMD and diabetic retinopathy in terms of drug development. For this reason, it is likely that the immunotherapeutic medications for uveitis will continue to be driven by indications for other specialties (e.g. rheumatology, transplant medicine, hematology/oncology), and the off-label use of medications will continue for patients with complex ocular inflammatory conditions.

The proven non-inferiority of bevacizumab relative to its FDA-approved counterpart sets a precedent for the off-label use of other biologics in the eye. It is important to consider the historical fact that since bevacizumab and ranibizumab share a common molecular origin, many of the initial assumptions about intravitreal bevacizumab treatment were derived from available data for ranibizumab, and the initial dosing of bevacizumab was based on the posology of ranibizumab.<sup>9</sup> By contrast, the recent findings of toxicity of intravitreal infliximab underscore the importance of careful attention to appropriate dosing and preclinical assessment of toxicity. Simply assuming that clinically available concentrations and preparations of drugs will be optimal and safe for intravitreal therapy is unreasonable and potentially dangerous.

The CATT trial results, obtained from a multicenter, prospective study touches on many topics that are apropos for the uveitis and retinal specialist and provides lessons on the manner in which we should proceed with delivery of FDA-approved off-label medications. Besides demonstrating no adverse local or systemic safety signals clearly related to the use of bevacizumab versus ranibizumab at the one-year time-point<sup>1</sup>, the efficacy data from both bevacizumab- and ranibizumab-treated patients illustrates how an understanding of mechanism and pharmacokinetics allows physicians to dramatically improve vision and quality of life of patients with wet AMD. Although the type of inflammatory pathways may differ between AMD and uveitis, the rapid increase in clinical trials evaluating biologic therapies and increasing overlap in terms of treatment options reinforces the concept that specific intravitreal biologic therapies will continue to be developed and implemented. Implicit to this discussion is the necessity to continue unraveling the inflammatory, angiogenic, and wound healing pathways central to each specific disease process. The CATT trial data, in combination with lessons from other intravitreal biologics used previously for uveitis (i.e. rituximab and infliximab), are reminders that although additional off-label use of immunotherapeutic targets for uveitis will likely come our way, our enthusiasm for these agents should be tempered by judicious and rigorous safety monitoring for both patient benefit and patient protection.

## Acknowledgments

*Funding/Support:* Supported by Intramural funding from the National Eye Institute, National Institutes of Health (RBN), an unrestricted grant from Research to Prevent Blindness (SY, Emory Eye Center).

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Table 1

Local and systemic biologics for age-related macular degeneration (AMD)\*

Medication (Study acronym)	Major pathways affected (e.g. complement, cytokine)	Specific Mechanism	Method of Drug Delivery	Disease Target	Clinical Trial Design (Clinical trial identifier)	Status
POT-4 (ASaP)	Complement	Complement inhibition	Intravitreal	Wet AMD with subfoveal choroidal neovascularization (CNV)	Phase 1, prospective, uncontrolled, dose-escalating pilot study	Completed
Eculizumab (COMPLETE)	Complement	C5 complement inhibition	Intravenous infusion	Dry AMD – Drusen and GA cohorts	Phase 2, randomized, double-arm, double-masked study evaluating safety and efficacy	Ongoing, not recruiting
LFG316	Complement	Unknown	Intravitreal	Wet AMD with CNV or dry AMD with geographic atrophy (GA)	Phase 1, multicenter, open-label, single ascending dose study	Recruiting
Palomid 529	mTOR	Mammalian target of rapamycin (mTOR) inhibition	Subconjunctival	Wet AMD	Phase 1, unmasked study to assess safety and tolerability	Recruiting
Volociximab	Integrin	Alpha 5 Beta 1 integrin antagonist	Intravitreal	Wet AMD	Phase 1, non-randomized study to evaluate safety, tolerability and pharmacokinetics	Ongoing, not recruiting
JSM6427	Integrin	Alpha 5 Beta 1 integrin antagonist	Intravitreal	Wet AMD	Phase 1, open-label study of safety, tolerability and pharmacokinetic profile	Completed
Aflibercept/VEGF-Trap (VIEW 2)	VEGF	VEGF antagonist	Intravitreal	Wet AMD	Phase III, multicenter, randomized, double-masked, safety/efficacy study	Ongoing, not recruiting
Anti-VEGFR vaccine therapy	VEGF	HLA-A*2402 restricted epitope peptides VEGFR1 and VEGFR2 emulsified with Montaimde ISA51	Subcutaneous vaccination/injection	Wet AMD	Phase I, open-label, uncontrolled study	Unknown
MP0112	VEGF	Potentially long-acting VEGF inhibitor	Intravitreal	Wet AMD	Phase I/II, open label, dose-escalating, multicenter safety and efficacy study	Study terminated
KH902	VEGF	Recombinant human VEGF Receptor-Fc Fusion protein	Intravitreal	Wet AMD	Phase III, multicenter, randomized, double-masked safety and efficacy study	Recruiting (China)**
Pazopanib	VEGF, PDGF	Tyrosine kinase inhibitor of multiple receptors including VEGF receptors and platelet-derived growth factor receptors	Topical	Wet AMD	Phase IIb, double-masked, dose-ranging study of pazopanib eye drops versus intravitreal ranibizumab	Ongoing, not recruiting
iSONEP (Sonepeizumab, LT1009)	Antibody-mediated inhibition of angiogenesis	SIP inhibition, which modulates AMD-associated angiogenesis, inflammation, and fibrosis	Intravitreal	Wet AMD	Phase I, open label, dose-escalating, multicenter, safety and efficacy study	Unknown
AA V2-sFLT01	Gene-based angiogenesis inhibition	Gene transfer agent targeting angiogenesis inhibition	Intravitreal	Wet AMD	Phase I, open-label, multicenter, dose-escalating safety and tolerability study	Recruiting
rAAV .sFlt-1	Gene-based angiogenesis inhibition	Gene transfer agent targeting angiogenesis inhibition	Subretinal injection	Wet AMD	Phase I/II controlled, dose-escalation safety/efficacy study	Recruiting
Adalimumab	Pro-inflammatory cytokine	TNF inhibition with humanized monoclonal anti-TNF antibody	Intravitreal	Wet AMD not responding to ranibizumab	Phase II, open label, single-center, safety and efficacy study	Recruiting

Medication (Study acronym)	Major pathways affected (e.g. complement, cytokine)	Specific Mechanism	Method of Drug Delivery	Disease Target	Clinical Trial Design (Clinical trial identifier)	Status
Infliximab	Pro-inflammatory cytokine	TNF inhibition with chimeric	Intravitreal	Wet AMD, diabetic macular edema	Phase I, open label, single-center safety and tolerability study	Unknown
Daclizumab, infliximab, sirolimus	Pro-inflammatory cytokine (daclizumab, infliximab), mTOR (sirolimus)	IL-2 receptor inhibition (daclizumab), TNF-inhibition (infliximab), and mTOR inhibition (sirolimus)	Systemic	Wet AMD	Phase II, open label, randomized, placebo-controlled, single-center safety and efficacy study of systemic immunosuppression combined with anti-VEGF therapy	Completed
CNTO2476	Cell-based therapy	Human umbilical tissue-derived cells (CNTO 2476)	Subretinal	Dry AMD with GA	Phase I/IIa, multicenter, randomized, dose-escalation, fellow-eye controlled safety and efficacy study	Recruiting
MA09-hRPE	Cell-based therapy	Transplantation of embryonic stem cell (hESCR) derived RPE cells	Subretinal transplantation of hESC derived RPE (MA09-hRPE) cells	Advanced dry AMD	Phase I/II, open-label, multicenter, safety and tolerability study	Recruiting

\* Summary of ongoing clinical trials involving biologic therapies for age-related macular degeneration (AMD, incomplete list). This table does not include the prior clinical trials of ranibizumab and bevacizumab

\*\* Phase I/II studies were completed previously. A dose-ranging Phase II study is ongoing, but not recruiting.

Abbreviations hESC human embryonic stem cells S IP inhibition Sphingosine-1-phosphate antibody PDGF Platelet-derived growth factor