Published in final edited form as:

Retina. 2010 January ; 30(1): 1–5. doi:10.1097/IAE.0b013e3181cde727.

More Questions Than Answers: A Call for a Moratorium on the Use of Intravitreal Infliximab Outside of a Well-Designed Trial

Jose S. Pulido, MD, MS, MPH, MBA,

Division of Ophthalmology Mayo Clinic College of Medicine Rochester, Minnesota

Jose E. Pulido, BSE,

University of Pennsylvania School of Medicine Philadelphia, Pennsylvania

Clement J. Michet, MD, and

Department of Internal Medicine, Rheumatology Division Mayo Clinic and Foundation Rochester, Minnesota

Richard G. Vile, PhD

Departments of Molecular Medicine and Immunology Mayo Clinic College of Medicine Rochester, Minnesota

Antibody Therapy for Vitreoretinal Diseases

The success of intravitreal bevacizumab (~149 kD) was unexpected because the initial studies by Ferrara, comparing ranibizumab (48 kD) with larger monoclonal antibodies, suggested that larger antibodies would not penetrate the retina.¹ Interestingly, the study did not compare the penetration of ranibizumab directly to bevacizumab. The reason was apparently because the authors noted that intravitreal bevacizumab was sometimes associated with intraocular inflammation. Therefore, the authors compared exactly the same milligram amounts of ranibizumab with trastuzumab (145.5 kD), a Herceptin receptor2 antibody. The authors found greater penetration of ranibizumab than trastuzumab in the retina and believed that this showed that large antibodies did not penetrate the retina. Unfortunately, the study was flawed in that ranibizumab has a much smaller molecular weight than trastuzumab (48 versus 145.5) so that for the same amount of milligrams, they were not comparing a similar number of molecules of the 2 compounds, but rather they were comparing the penetration of >3 times as much ranibizumab than trastuzumab.

More recent studies have shown that not only does intravitreal bevacizumab penetrate the retina, but it is also efficacious in treating preretinal, retinal, and choroidal neovascularization.^{2–4} The efficacy of intravitreal bevacizumab is such that it is taking a large multicenter trial to actually determine if there is a difference in efficacy between bevacizumab and its smaller relative, ranibizumab.⁵

Another large monoclonal antibody, rituximab (143.9 kD), a monoclonal antibody that binds CD20, has also shown ability to penetrate the retina.⁶ In addition, preliminary studies have shown some efficacy in treating primary intraocular lymphoma as well as secondary intraocular lymphoma.⁷ Further studies have to be performed to confirm these early findings.

Copyright © by Ophthalmic Communications Society, Inc.

Reprint requests: Jose S. Pulido, MD, MS, MPH, MBA, Department of Ophthalmology, Mayo Clinic, 200 First Street Southwest, Rochester, NY 55902; pulido.jose@mayo.edu.

None of the authors have a proprietary interest.

There are presently hundreds of monoclonal antibodies in some phase of development for clinical use and many might have ocular use as well. In light of the ability of intravitreal monoclonal antibodies to penetrate the retina and to show clinical efficacy, there is a palpable excitement in trying to find the next agent that will make a difference in the care of patients with eye disease.

Tumor Necrosis Factor Alpha and Inflammation

Recent published peer-reviewed articles have looked at the systemic use of infliximab for uveitis and, more recently, described the clinical findings in very small clinical trials of intravitreal infliximab (molecular weight 149 kD).^{8,9} The reasons why there is now an interest in the intraocular use of infliximab need to be discussed as well as what the conflicting findings show.

Infliximab is a chimeric murine-based monoclonal antibody targeted to tumor necrosis factor alpha (TNF α) with 70% human homology. The other commercially available TNF α inhibitors are adalimumab and golimumab, monoclonal antibodies as well; certolizumab, which is a monoclonal antibody that combines the Fab fragment of the TNF α antibody with polyethylene glycol; and etanercept, a soluble receptor that traps the TNF α . Tumor necrosis factor alpha is a 26-kD proinflammatory cytokine of the TNF superfamily of proteins, a family that involves 19 different ligands and 30 different receptor proteins.¹⁰ Tumor necrosis factor alpha binds to TNF receptors on the cell surface of inflammatory cells, including lymphocytes, neutrophils, and endothelial cells, all forms of renal cells and smooth muscle cells, and exacerbates inflammation. The release of TNF α during infectious processes is helpful in causing better trafficking of neutrophils to the site of infection by causing vasodilation, adhesion of neutrophils to the endothelium, enhanced microbial killing by the neutrophils, and increased expression of class I and class II major histocompatibility complex proteins. Abnormally high levels cause septic shock, release of other cytokines, cachexia, and heart failure.

Tumor necrosis factor alpha has a form that is cell-bound, but it can be cleaved from the cell membrane by an enzyme called TNF α -converting enzyme (a membrane-bound disintegrin metalloproteinase that processes the membrane-associated cytokine pro-TNF α to a soluble form). The soluble form binds to TNF receptor 1, which is the most common receptor, and TNF receptor 2, which is mainly found on endothelial cells^{10,11} and forms an active trimer. Etanercept is a soluble dimeric TNF receptor that binds both TNF α and TNF β and thus prevents TNF from binding to the cell-bound receptors. Once TNF α binds to its cell surface receptor, a cascade of proinflammatory, oxidative, and apoptotic events occurs in the activated cell that not only affects the cell but also other cells.^{8,12} Binding of the transmembrane form by TNF α inhibitors also inhibits the production of cytokines and induces apoptosis of the cell.¹³

The TNF α inhibitors have been used for a variety of inflammatory diseases. Recent reviews have evaluated the published trials on the use of these agents.^{11,14} The studies have shown efficacy of TNF α inhibitors in rheumatoid arthritis, Crohn disease, psoriatic arthritis, and juvenile chronic arthritis.^{11,14} It has been used in other situations, including uveitis from Behçet as well other forms of uveitis with apparent success, although the studies tend to be a small series and nonrandomized.^{15,16}

Aside from traditional inflammatory diseases, TNF α appears to have a role in some of the complications of diabetes mellitus.¹⁷ For instance, in diabetic nephropathy, there is elevated TNF α in the kidney and in the circulating blood.¹⁸ The inflammation produced by the TNF α may further damage the kidney. In a murine model of diabetes, there was an increase of

TNF α in the urine, and inhibition of TNF α by infliximab reduced TNF α excretion and also decreased albuminuria, a sign of renal damage.¹⁹ Elevated levels of TNF α have also been associated with diabetic neuropathy.²⁰ So, there might be a rationale for the use of TNF α inhibitors in the treatment of some noninflammatory diseases.

The Adverse Effects of Tumor Necrosis Factor Alpha Inhibitors

Systemic TNF α inhibitors may cause significant complications, especially with long-term use.^{21–23} The severe adverse events can be divided into those that happen for the entire class of agents in general and those that occur for a specific agent. Both of these types of adverse events are numerous. General severe adverse events can be further subclassified into development of infectious diseases, development of malignancies, infusion reactions, and development of autoimmunity.^{22–24} It is ironic that agents in the short term appear to decrease inflammation and might help in some cases of cancer, whereas in the long term, these might cause inflammation and cancer.

The development of tuberculosis is an important consideration with the use of the TNF α inhibitors, and the current recommendation is that a patient who has evidence of a positive tuberculin test or interferon gamma release assay should be treated for latent tuberculosis before using these agents.¹⁴ The odds of development of tuberculosis with the use of TNF α inhibitors is approximately four times than that of other agents. The risk of a hematologic complication is also increased compared with the use of other agents. As it is, the Food and Drug Administration has issued a black box warning on the systemic use of TNF α inhibitors in children because of their risk of causing malignancies.²⁵ There is some thought that the TNF α inhibitors might also be associated with an increased risk of solid malignancies, and it is interesting to note that in a recent prospective series of 32 patients who were treated with infliximab for uveitis, 2 developed solid malignancies.^{16,26} The use of infliximab in patients with rheumatoid arthritis increases the risk of development of an antinuclear antibody from 28% to 80%. Antidouble-stranded DNA antibodies increased from 0% to 15% and anticardiolipin antibodies increased from 16% to 26%. In addition, the patients can develop human antichimeric antibodies (HACAs) and human antimouse antibodies with the use of infliximab and human antihuman antibodies with the use of adalimumab or etanercept.^{11,13,14} In the prospective study noted previously, of >32 patients with uveitis who were treated with infliximab, 3 developed a lupus-like illness.¹⁶

Infusion reactions are the most common adverse event and many times require pretreatment with histamine antagonists and systemic corticosteroids.¹⁴ In a few patients, they can develop severe anaphylaxis. It appears that those who develop infusion reactions after an infusion of infliximab have a higher risk of having HACAs, and the infliximab appears to have less effect in those who develop the antibodies.^{13,27,28}

Infliximab Use in Ocular Diseases

The use for ocular diseases initially started with the use of systemic infliximab for cases of uveitis, including those associated with Behçet.^{8,29–32} It has had good results in decreasing the uveitis, and it was noted to improve the concomitant cystoid macular edema, although there are now concerns of systemic adverse effects after its long-term systemic use for ocular diseases.^{30–32} Subsequently, it was noted that in a few patients with ankylosing spondylitis or rheumatoid arthritis who had coincident exudative age-related macular degeneration, the intravenous infusion of infliximab caused regression of the choroidal neovascularization.³² In addition, they then gave it as two infusions in patients with refractory diabetic macular edema.³³ Four patients were given at least two and up to four infusions, and there appeared to be improvement in this small series in vision and macular

edema. They stated that there were no complications of the infusion, but they do not mention if laboratory evaluations were performed.

Because of these preliminary encouraging results, the same group decided to use 1 or 2 mg infliximab intravitreally in 3 patients.⁹ The patients had choroidal neovascularization secondary to age-related macular degeneration that was refractory to ranibizumab. The first patient had an injection of 1 mg intravitreal infliximab with an improvement of vision from 20/200 to 20/100, but there was a 20% reduction of macular swelling as noted by optical coherence tomography after 8 weeks. A second injection of 2 mg was given with complete regression of intra- and subretinal fluid at 6 months, but 1 month later, the fluid returned. The vision also improved to 20/40, but then when the fluid recurred, the vision dropped again to 20/100, showing that in at least some patients, this is not permanent therapy, an important consideration we will discuss later. Subsequently, they decided to use it in two other patients. The second patient had vision of 20/200 before treatment and a macular thickness of 512 μm . Two intravitreal injections of 2 mg each were given 8 weeks apart. After the second injection, they noted “vitreous opacities without inflammation,” which they attributed to minor vitreous hemorrhage. Again, the thickness of the macula markedly improved to 184 μm , and the vision improved to 20/70 2 months after the second injection. No further follow-up was noted. The third patient had initial vision of 20/70 and after 2 injections, the vision improved to 20/30. As with the cases the authors reported with systemic therapy, no mention is made about testing for HACAs or other autoantibodies.

The accompanying editorial raised some questions, including whether the patients had a fair trial of ranibizumab before they were labeled as refractory to the drug and also the stability of infliximab for multiple uses.³⁴

In this journal, there are two reports on infliximab. One attempts to answer the question of the stability of the agent over time.³⁵ The authors conclude that for a 6-week period, the drug stayed stable at 4°C. They did not evaluate the effect of refrigeration on sterility and this still needs to be evaluated. In addition, there are some concerns about the study because they used a very sensitive method. Small errors would amount for some uncertainty in the concentrations such that there is probably a 10% chance of variability in the possible concentration of the agent and so at 6 weeks, the concentration is at least 90% of the starting concentration.

New Data, but Questions Remain Unanswered

A more important question is whether we should be using this agent. The second report is disconcerting.³⁶ In this report, the authors obtained the approval of the Food and Drug Administration, Investigational New Drug and Institutional Review Board to evaluate the use of 0.5 mg infliximab intravitreally in 4 patients with macular edema, either secondary to diabetic macular edema or to choroidal neovascularization from age-related macular degeneration. A second injection was offered to the patient if they showed a favorable response at 6 weeks. Vision, electroretinograms, and optical coherence tomography were examined. In addition, and different from the other report on intravitreal infliximab, the patients were tested for the presence of human antimouse antibodies or HACAs at 6 months. It is important to note that the dose used was one half to one fourth the dose used by Theodossiadis et al.⁹ Three of the four in this series developed inflammation after the infliximab. Only one had better vision and less macular edema. In addition, 3 of the 4 patients were noted to have HACAs but no human antimouse antibodies at 6 months.

Questions arise from this study that need further answers before this agent can be used outside of a well-designed study. Although testing for HACAs has become quite standard,

similar to other tests when they were first used frequently, there is variability in the methods used to test for it as well as the sensitivity and specificity of each test.³⁷ It would have been reassuring to have performed testing for HACAs before and after treatment. This would have added to the conclusion that it was purely a response to the intraocular infliximab and not a false-positive. The fact that most patients had prior treatments with bevacizumab or ranibizumab as well and did not have good responses further adds to the need of having had a baseline test for HACAs. Although systemic bevacizumab has not been associated with the development of human antihuman antibodies,³⁸ it is not known whether intraocular bevacizumab might cause development of human antihuman antibodies, and this needs to be investigated; but if it does, could the present study's test for HACAs have a cross-reaction with preexisting human antihuman antibodies if they were present? Again, testing before and after initiation of treatment would have answered this lingering question.

Interestingly, two of the patients treated by the authors of this study had prior inflammatory reactions after the use of intraocular triamcinolone or bevacizumab. Could this have primed them to react to the infliximab reactions and could this be why this study shows a much higher incidence of inflammatory reactions than the study by Theodossiadis, which did not report such cases?

These authors also used a dose that was one fourth to one half the dose used by Theodossiadis. When infliximab is systemically used, higher systemic doses of infliximab paradoxically have a smaller chance of developing HACAs.^{13,14} Could Theodossiadis et al⁹ have inadvertently found that their higher dose was a safer dose than the dose used in this study or could it be that because they did not look for HACAs, they did not find HACAs?

Because this agent does not appear to cause a permanent cure, the single, let alone the repeated, use of this agent is disconcerting. The authors are to be commended for putting the brakes on an intravitreal agent that might cause more harm than good. Following this report, it is our responsibility to use intravitreal infliximab only in the context of a well-monitored and thought-out Institutional Review Board-approved trial.

Acknowledgments

Supported in part by an unrestricted grant from Research to Prevent Blindness Inc., New York, New York. This work is supported by a grant from the National Institute of Health (R01CA107082).

References

1. Ferrara N, Damico L, Shams N, Lowman H, Kim R. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. *Retina*. 2006; 26:859–870. [PubMed: 17031284]
2. Bakri SJ, Snyder MR, Reid JM, Pulido JS, Singh RJ. Pharmacokinetics of intravitreal bevacizumab (Avastin). *Ophthalmology*. 2007; 114:855–859. [PubMed: 17467524]
3. Bakri SJ, Risco M, Edwards AO, Pulido JS. Bilateral simultaneous intravitreal injections in the office setting. *Am J Ophthalmol*. 2009; 148:66–69. [PubMed: 19403114]
4. Ciulla TA, Rosenfeld PJ. Anti-vascular endothelial growth factor therapy for neovascular ocular diseases other than age-related macular degeneration. *Curr Opin Ophthalmol*. 2009; 20:166–174. [PubMed: 19381089]
5. Landa G, Amde W, Doshi V, et al. Comparative study of intravitreal bevacizumab (Avastin) versus ranibizumab (Lucentis) in the treatment of neovascular age-related macular degeneration. *Ophthalmologica*. 2009; 223:370–375.
6. Pulido JS, Bakri SJ, Valyi-Nagy T, Shukla D. Rituximab penetrates full-thickness retina in contrast to tissue plasminogen activator control. *Retina*. 2007; 27:1071–1073. [PubMed: 18040247]

7. Itty S, Pulido JS. Rituximab for intraocular lymphoma. *Retina*. 2009; 29:129–132. [PubMed: 19202422]
8. Theodossiadis PG, Markomichelakis NN, Sfrikakis PP. Tumor necrosis factor antagonists: preliminary evidence for an emerging approach in the treatment of ocular inflammation. *Retina*. 2007; 27:399–413. [PubMed: 17420690]
9. Theodossiadis PG, Liarakos VS, Sfrikakis PP, Vergados IA, Theodossiadis GP. Intravitreal administration of the anti-tumor necrosis factor agent infliximab for neovascular age-related macular degeneration. *Am J Ophthalmol*. 2009; 147:761–763. [PubMed: 19376327]
10. Croft M. The role of TNF superfamily members in T-cell function and diseases. *Nat Rev Immunol*. 2009; 9:271–285. [PubMed: 19319144]
11. Chen YF, Jobanputra P, Barton P, et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. *Health Technol Assess*. 2006; 10:1–229.
12. Zhang DW, Shao J, Lin J, et al. RIP3, an energy metabolism regulator that switches TNF-induced cell death from apoptosis to necrosis. *Science*. 2009; 325:332–336. [PubMed: 19498109]
13. Wong M, Ziring D, Korin Y, et al. TNF α blockade in human diseases: mechanisms and future directions. *Clin Immunol*. 2008; 126:121–136. [PubMed: 17916444]
14. Lin J, Ziring D, Desai S, et al. TNF α blockade in human diseases: an overview of efficacy and safety. *Clin Immunol*. 2008; 126:13–30. [PubMed: 17916445]
15. Tabbara KF, Al-Hemidan AI. Infliximab effects compared to conventional therapy in the management of retinal vasculitis in Behçet disease. *Am J Ophthalmol*. 2008; 146:845–850. [PubMed: 18929351]
16. Suhler EB, Smith JR, Giles TR, et al. Infliximab therapy for refractory uveitis: 2-year results of a prospective trial. *Arch Ophthalmol*. 2009; 127:819–822. [PubMed: 19506209]
17. Navarro-Gonzalez JF, Jarque A, Muros M, Mora C, García J. Tumor necrosis factor- α as a therapeutic target for diabetic nephropathy. *Cytokine Growth Factor Rev*. 2009; 20:165–173. [PubMed: 19251467]
18. Wong CK, Ho AW, Tong PC, et al. Aberrant activation profile of cytokines and mitogen-activated protein kinases in type 2 diabetic patients with nephropathy. *Clin Exp Immunol*. 2007; 149:123–131. [PubMed: 17425653]
19. Moriwaki Y, Inokuchi T, Yamamoto A, et al. Effect of TNF- α inhibition on urinary albumin excretion in experimental diabetic rats. *Acta Diabetol*. 2007; 44:215–218. [PubMed: 17767370]
20. Gonzalez-Clemente JM, Mauricio D, Richart C, et al. Diabetic neuropathy is associated with activation of the TNF- α system in subjects with type 1 diabetes mellitus. *Clin Endocrinol (Oxf)*. 2005; 63:525–529. [PubMed: 16268804]
21. Nair B, Raval G, Mehta P. TNF- α inhibitor etanercept and hematologic malignancies: report of a case and review of the literature. *Am J Hematol*. 2008; 83:345. [PubMed: 18318433]
22. Ramos-Casals M, Brito-Zero P, Munõz S, et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Medicine (Baltimore)*. 2007; 86:242–251. [PubMed: 17632266]
23. Fulchiero GJ Jr, Salvaggio H, Drabick JJ, et al. Eruptive latent metastatic melanomas after initiation of antitumor necrosis factor therapies. *J Am Acad Dermatol*. 2007; 56:S65–S67. [PubMed: 17434043]
24. Wollina U, Hansel G, Koch A, Schönlebe J, Köstler E, Haroske G. Tumor necrosis factor- α inhibitor-induced psoriasis or psoriasiform exanthemata: first 120 cases from the literature including a series of six new patients. *Am J Clin Dermatol*. 2008; 9:1–14. [PubMed: 18092839]
25. Information for healthcare professionals: tumor necrosis factor (TNF) blockers (marketed as Remicade, Enbrel, Humira, Cimzia, and Simponi). Food and Drug Administration; 2009. Available at: www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm174474.htm [Accessed November 30, 2009]
26. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA*. 2006; 295:2275–2285. [PubMed: 16705109]

27. Haraoui B, Cameron L, Ouellet M, White B. Anti-infliximab antibodies in patients with rheumatoid arthritis who require higher doses of infliximab to achieve or maintain a clinical response. *J Rheumatol*. 2006; 33:31–36. [PubMed: 16395747]
28. Calabrese LH. Molecular differences in anticytokine therapies. *Clin Exp Rheumatol*. 2003; 21:241–248. [PubMed: 12747285]
29. Ohno S, Nakamura S, Hori S, et al. Efficacy, safety, and pharmacokinetics of multiple administration of infliximab in Behçet's disease with refractory uveoretinitis. *J Rheumatol*. 2004; 31:1362–1368. [PubMed: 15229958]
30. Sfikakis PP, Theodossiadi PG, Katsiari CG, Kaklamanis P, Markomichelakis NN. Effect of infliximab on sight-threatening panuveitis in Behçet's disease. *Lancet*. 2001; 358:295–296. [PubMed: 11498218]
31. Sfikakis PP, Kaklamanis P, Elezoglou A, et al. Infliximab for recurrent sight-threatening ocular inflammation in Adamantiades–Behçet's disease. *Ann Intern Med*. 2004; 140:404–406. [PubMed: 14996689]
32. Markomichelakis N, Theodossiadi PG, Pantelia E, Papaefthimiou S, Theodossiadi GP, Sfikakis PP. Infliximab for chronic cystoid macular edema associated with uveitis. *Am J Ophthalmol*. 2004; 138:648–650. [PubMed: 15488796]
33. Sfikakis PP, Markomichelakis N, Theodossiadi GP, Grigoropoulos V, Katsilambros N, Theodossiadi PG. Regression of sight-threatening macular edema in type 2 diabetes following treatment with the anti-tumor necrosis factor monoclonal antibody infliximab. *Diabetes Care*. 2005; 28:445–447. [PubMed: 15677814]
34. Rosenfeld PJ, Goodman KW. When is off-label drug use in the patient's best interest? *Am J Ophthalmol*. 2009; 147:761–763. [PubMed: 19376327]
35. Beer PM, Wong SJ, Schartman JP, Kulas KE, Hartman CL, Giganti M, et al. Infliximab stability after reconstitution, dilution, and storage under refrigeration. *Retina*. 2010; 30:81–84. [PubMed: 20010324]
36. Giganti M, Beer PM, Lemanski N, Hartman C, Schartman J, Falk N. Adverse events following intravitreal infliximab (Remicade). *Retina*. 2010; 30:71–80. [PubMed: 19996827]
37. Aarden L, Ruuls SR, Wolbink G. Immunogenicity of anti-tumor necrosis factor antibodies-toward improved methods of anti-antibody measurement. *Curr Opin Immunol*. 2008; 20:431–435. [PubMed: 18619538]
38. Hwang WY, Foote J. Immunogenicity of engineered antibodies. *Methods*. 2005; 36:3–10. [PubMed: 15848070]