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Review Article

The Role of Non-Anti-TNFα Biologics in Refractory Non-Infectious Uveitis: A Literature Review

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Abstract

Uveitis, or inflammation of the pigmented structures of the eye, is a common ocular complaint with a variety of etiologies. One common etiology, often called non-infectious uveitis, is as a systemic manifestation of auto-immune disease, including inflammatory bowel disease, Behcet's disease, juvenile idiopathic arthritis, and more. First line treatments for non-infectious uveitis include corticosteroids and second line therapy includes immunomodulatory agents such as methotrexate and azathioprine. When uveitis is refractory to these treatments, biologic therapies are effective treatments, with the two most widely studied and effective agents being anti-TNFα drugs Adalimumab and Infliximab. However, when anti-TNFα agents fail, there are limited guidelines as to the next step in treatment. The authors, using a difficult case of IBD-associated non-infectious uveitis refractory to first, second, and third line therapies as the impetus, conducted a review of the literature to examine the current evidence for non-anti-TNFα biologics for treatment of uveitis.

Using a literature search through PubMed, MEDLINE, and Google Scholar, the authors identified scholarly articles on all classes of non-anti-TNFα biologics. Evidence for most classes were limited. Tocilizumab, an IL-6 inhibitor has the most promising evidence, including a randomized control trial that demonstrates effectiveness in treating non-infectious uveitis. Other drugs that have shown somewhat encouraging evidence based on case series or case reports include Adabacept, Tofacitinib, Baricitinib, Secikinumab, Ustekinumab, Anakinra, Canakinumab and Rituximab.

Keywords: *Non-Anti-TNFα; Refractory Non-Infectious Uveitis; Adalimumab and Infliximab*

Introduction

Uveitis is a general term used to denote inflammation of the iris, choroid and ciliary body, but is also commonly used to describe inflammation of any intraocular structure [1]. If left untreated, uveitis can lead to vision-threatening complications such as cataract formation, glaucoma and retinal edema [2], constituting up to 15% of all cases of blindness in developed countries [3]. Uveitis can be caused both by infectious and non-infectious idiopathic causes and is seen as manifestations of many systemic inflammatory conditions. These conditions include inflammatory bowel disease (IBD), juvenile idiopathic arthritis (JIA), sarcoidosis, spondyloarthropathies (SA), rheumatoid arthritis (RA), and Behçet's disease (BD). Although the pathogenesis of non-infectious uveitis (NIU) has not been completely elucidated, it is believed that the inflammatory response is medicated by CD4+ T-helper cells (Th1 phenotype), leading to or coinciding with an upregulation in pro-inflammatory cytokines like IL-1, IL-2, IL-12, IL-17, TNF-α, and INF-γ [4]. NIU is often very difficult to treat and requires immunosuppressive therapy to control the ocular inflammation. Corticosteroids (topical, injection or oral) are first line treatment of uveitis,

although prolonged treatment is often precluded as it is associated with adverse side effects, such as increased intraocular pressure [5]. When inflammation is severe or persistent on steroids, second line therapy is non-corticosteroid immunomodulatory therapy (NCSIT), which includes immunosuppressive drugs methotrexate, azathioprine, mycophenolate moxetil, tacrolimus, and cyclosporine; however, these have been shown to have mixed efficacy [6,7]. Specific indicators for initiation of NCSIT were outlined in the FOCUS trial and include structural damage, such as retinal detachment, active disease on high dose steroids, and severity of symptoms, among others [7].

Biotherapy, specifically targeting tumor necrosis factor alpha (TNFα) has shown to be very effective in treating uveitis when disease is not controlled on steroid or NCSI treatment [8]. TNFα is a pro-inflammatory master cytokine produced by immune and endothelial cells which induces the proliferation and migration of inflammatory cells, the secretion of additional pro-inflammatory cytokines (IL-1, IL-6) and the release of nitric oxide by macrophages [9]. Infliximab (Remicade) and Adalimumab (Humira) are the most commonly used Anti-TNFα agents used in the treatment of systemic inflammatory conditions and NIU. A recent retrospective study of 21 patients with NIU showed that treatment with anti-TNFα (Infliximab and Adalimumab) therapies led to both initial and sustained control of the ocular inflammation with a response rate 80.9% at three months (M3) and 83.3% at one year (M12) [10]. Furthermore, these patients had previously uncontrolled ocular inflammation despite the use of other therapies. In other published works, the initial efficacy of all anti-TNFα drugs was more variable, ranging from 55.6% - 100% at M3 [11,12]. However, the excellent long-term (M12) efficacy of Infliximab is consistent amongst existing published studies [13,14]. Furthermore, a large retrospective multicenter study compared the efficacy of infliximab and adalimumab for the treatment of refractory NIU and demonstrated that and infliximab and adalimumab appeared to be equivalent in terms of efficacy [15].

However, when anti-TNFα drugs fail, newer biologic agents are being used to target and downregulate interleukin and inflammatory cell signalling. These drugs include: Tocilizumab (anti-IL-6 humanized antibody), Secukinumab (Anti-IL-17 monoclonal antibody (mAb)), Canakinumab (Anti-IL -1β), Anakinra (IL-1 receptor antagonist), Ritximab (Anti-CD20 antibody) and Abatacept (T-cell co-stimulation modulator).

The authors of this study experienced a difficult case of a patient with a 20 year history of inflammatory bowel disease, specifically ulcerative colitis, who developed severe uveitis with eye pain, blurry vision, and photophobia bilaterally. The patient developed recurrence of their symptoms after every instance of steroid taper and cannot stay on long term steroids due to the development of elevated intraocular pressures. Additionally, the patient has been trialed on numerous biologic treatments, including infliximab, adalimumab, golimumab and ustakinumab. Thus, the authors of this study used this case as the impetus to examine the current climate of non-anti-TNFα biologics in the treatment of non-infectious uveitis.

Methods

The patient's demographic and clinical encounter information was obtained from their Ophthalmologists and Gastroenterologist with written consent from the patient.

A literature search was conducted through PubMed, MEDLINE, and Google Scholar databases using combinations of the following search terms: "uveitis," "non-infectious uveitis," "biologics," "ant-TNF," "inflammatory bowel disease," "tocilizumab," "abadacept," "tofacitinib," "baricitinib," "secukinumab," "ixekizumab," "ustekinumab," "anakinra," "canakinumab," "vedolizumab", and "rituximab".

Discussion tocilizumab

Tocilizumab (TCZ) is a monoclonal antibody specifically targeted to the receptors of Interleukin- 6 (IL-6), a cytokine produced by many white blood cells and that has been found in intraocular fluid of eyes with uveitis [16]. Tocilizumab has FDA approval for treatment of rheumatoid arthritis, JIA and giant cell arteritis but not for NIU. However, there have been several case reports, case series and literature

reviews that studied its efficacy of TCZ. In two of these case reports, treatment with 8 mg/kg increase visual acuity and decreased macular edema due to NIU [17,18]. Interestingly, one study demonstrated that while TCZ can treat acute inflammation, it cannot repair chronic damage in the eye and subsequent vision loss from this damage [18].

A retrospective cohort study by Mesquida., *et al*. in 2014 studied central foveal thickness (CFT) and visual acuity in 11 eyes of patients with NIU treated with TCZ, all of whom failed immunosuppressive therapy and at least 1 biologic [19]. There was a significant decrease in CFT (550 μm ± 226 at baseline vs. 274 ± 56 at 1 year) and a significant increase in visual acuity (0.67 ± 0.53 logMAR at baseline to 0.4 ± 0.56 logMAR at 1 year), without any serious adverse events reported [19].

Finally, The STOP-UVEITIS study was a 2017 randomized clinical trial comparing two doses of Tocilizumab in patients with moderate NIU that measured systemic and ocular adverse events, mean change in BCVA, CFT, and vitreous haze (VH), all at month 6. Regarding adverse events, the most common systemic adverse event was sinus congestion and rhinorrhea, which was thought not to be attributed to the study drug [20]. Two patients receiving the high dose of Tocilizumab did develop low absolute neutrophil counts (ANC) after the first infusion. One patient exited the study, while the other's ANC resolved by the second treatment [20]. The most common ocular adverse event was elevated IOP, but similarly, none were thought to be related to Tocilizumab. Mean BCVA change was +8.22 letters in the two groups combined, and interestingly, the +10.9 and +5.5 in the low and high-dose groups respectively. The difference between the two groups was not statistically significant. Mean change in CMT was -83.88 microns in the two groups combines and -131.5 and -38.92 microns in the low and high-dose groups respectively. Again, the difference between the two groups was not statistically significant. Lastly, change in vitreous haze was -0.77 in both groups combined, and -0.63 and -0.91 in the low and high-dose groups respectively. Once more, the difference between the two groups was not significant. Thus, this study shows that patients with NIU treated with Tocilizumab had significantly better vision, less macular edema, and less vitreous haze after 6 months, and while not significant, trends showed that the low dose was more efficacious for vision and macular edema with less adverse events [20].

Abatacept

Abatacept (ABA) is a selective T cell co-stimulation modulator that acts to inhibit T cell activation by binding receptors CD80 and CD86 on antigen presenting cells. It is currently approved for use in treating RA and JIA. Multiple retrospective studies have been done on patients with uveitis secondary to JIA that is refractory to methotrexate, steroids, and DMARDs. In a 2015 study, uveitis inactivity was observed in 52.4% of patients during at least one follow up visit, but 72.7% showed a relapse at some point in follow-up [21].

A second study comparing ABA as second-line vs. first line agent was performed in 2016, demonstrating positive results. A total of 54.8% of patients showed remission after 12 months of treatment, with a higher, but not significant, proportion in the ABA as first line group. ABA also significantly reduced the number of flares in both groups [22].

A third study, a 2010 case series of seven patients, demonstrated the best evidence for ABA as a treatment for refractory NIU, with some caveats. Six of the seven patients treated with ABA had reduced inflammation, better visual acuity, and reduced number of flares after treatment of ABA, without any complications or adverse events. However, four patients were on corticosteroid drops at baseline; two were able to discontinue the drops completely, and two were able to taper to a lower dose. One patient was on methotrexate at baseline and continued on it throughout the study. As a result, the full effects of ABA alone are unclear [23].

These studies pertaining to ABA have limitations in the efficacy on overall NIU. All published literature on the topic of ABA and NIU is related to JIA-associated uveitis, with no data on uveitis related to any other inflammatory conditions such as RA, psoriatic arthritis, or IBD. Given the nature of JIA, these studies all study pediatric populations and there is no data on adult populations.

JAK inhibitors (Jakinibs)

Janus activator kinase (JAK) are enzymes in the JAK/signal transducer and activator of transcription (STAT) pathway that play a role in downstream activation of many cytokine receptors, including IL-2, IL-6 and IL-17 [24]. Tofacitinib (TOF) is an antibody and pan-JAK inhibitor that specifically targets JAK1 and JAK3 enzymes, with some action against JAK2 as well. It is currently approved to treat rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis [24]. Baricitinib is another Jakinib that specifically targets JAK1 and JAK 2. Studies have shown inhibition of autoimmune uveitis in mice models treated with TOF [25].

In a case report published in 2018 by Paley., *et al*. TOF was effective in combination with methotrexate to treat HLA-B27+, severe uveitis refractory to methotrexate monotherapy and steroid treatment. The symptoms also continued to be controlled on TOF monotherapy for 3 months after symptom resolution [26].

Finally, a 2020 case series of four patients with uveitis secondary to juvenile idiopathic arthritis (JIA) was published to show the efficacy of JAK inhibitors on uveitis. Both baricitinib (BAR), a JAK1 and JAK2 inhibitor, and TOF, demonstrated a reduction in uveal inflammation refractory to methotrexate, steroids, and ant-TNFa biologics, as well as a reduction in recurrence. According to this report, ocular symptoms responded better to the Jakinibs than articular symptoms, with no occurrence of systemic adverse events [27].

IL-17 antagonists

Secukinumab (SEC) and Ixekizumab (IXE) are monoclonal antibodies (mAb) that target cytokine Interleukin 17 (IL-17) and inhibits its binding to the IL-17 receptor. IL-17 plays an important role in inflammatory pathways in ankylosing spondylitis (AS), and there is evidence that IL-17 T-cells are elevated in HLA-B27 positive uveitis patients [28].

It has been reported in a proof-of-concept clinical study that Secukinumab demonstrated efficacy in 16 patients with active non-infectious uveitis [29]. However, SEC has since been more rigorously tested in 3 RCTs for BD patients with refractory uveitis: the SHIELD, ENDURE, and ENSURE trials. There were no statistically significant differences in uveitis recurrence or exacerbations between the SEC treatment groups and placebo groups in any of the studies [30]. However, the high amount of concomitant immunosuppressive therapy in both treatment and placebo groups throughout the study may have played a role in the lack of significant difference [30].

While there are no current clinical trials or case reports studying the use of IXE in NIU, studies show that it is beneficial in treating other inflammatory diseases mediated by IL-17 including AS and psoriatic arthritis. However, according to one recent systematic review on IXE, some adverse events were reported in clinical trials that IXE caused treatment-emergent anterior uveitis in patients with a prior history of uveitis. This suggests IXE should be avoided in patients with uveitis under further evidence for its use is found [31].

IL-23 antagonists

IL-23 is another inflammatory cytokine that plays a key role in differentiation of naïve T-cells to Th-17 helper cells, as well as in the activation of IL-17 production by Th-17 cells through a JAK/STAT pathway. Initially thought to be interchangeable with IL-17, there is evidence that it is increased in NIU and thus has become the target of some new biologics [32].

The most widely used IL-23 antagonist on the market is Ustekinumab (UST), which has FDA approval for treatment of moderate to severe Crohn's disease, moderate to severe plaque psoriasis, and psoriatic arthritis. In a 2013 case report by Baerveldt., *et al*. a patient with BD had remission of all BD symptoms after 36 months of treatment with UST33. In a second, 2017 case report by Mugghedu., *et al*. a patient with plaque psoriasis and subsequent NIU was treated with UST and had complete remission of their uveitis after 1 year of treatment [34].

There are two registered phase II RCTs to investigate the use of ustekinumab in treating NIU: the STELABEC trial, a 16 patient study investigating the use of UST in Behcet's disease (clinicaltrials.gov, NCT 0264858), and the STAR study, an eight patient trial studying the use of UST in uveitis (clinicaltrials.gov, NCT 02911116). Neither study has any published data to report at the time of this publication.

There are other IL-23 antagonists currently in Phase III trials for diseases such as Crohn's and psoriasis, but not yet any literature discussing their use in NIU.

IL-1 antagonists

IL-1 receptor antagonists like Anakinra and Canakinumab have shown some efficacy at treating a subset of Behcet's Disease (BD) patients with refractory uveitis [35]. In BD, IL-1 has been shown to be a proinflammatory cytokine that is critical in the disease's pathogenesis and its inhibition might be a promising option for novel therapeutics. In a multi-center retrospective observational study, BD patients who had refractory uveitis were treated with anti-IL-1 biologics Anakirna or Canakinumab. Both of these biologics demonstrated a rapid and sustained clinical efficacy while significantly reducing the number of intraocular flares, the relapse rate and the occurrence of retinal vasculitis [34].

Vedolizumab

Vedolizumab is another biologic agent used to treat IBD in patients resistant to TNF antagonists. It binds to α4β7 integrin which is expressed on activated gut T-lymphocytes, which blocks the interaction of α4β7 and mucosal adhesions in cell adhesion molecule 1 (MAdCAM-1) [36]. MAdCAM-1 is preferentially expressed on the endothelium of blood vessels in the gastrointestinal tract [35]. This GI-specific therapy for IBD helps reduce systemic side effects but may limit its effect on EIMs like uveitis. Despite this gut-specificity, limited case-study analysis has shown that treatment with Vedolizumab led to uveitis remission with no recurrence in a UC patient [37].

Rituximab

Rituximab, an mAb that targets the CD20 antigen on the B-cell surface used historically to treat lymphoma and RA, may be a promising treatment option for refractory non-infectious uveitis. A case-series of 8 patients with JIA-associated uveitis demonstrated that all patients achieved complete control of uveitis after one infusion of Rituximab [38]. Similarly, some evidence suggests that Abatacept, a T-cell co-stimulation modulator that binds to CD80 and CD86 on antigen- presenting cells, may also be a treatment option in refractory JIA-associated uveitis, although its prolonged effect was not proven and there was limited control of arthritis symptoms [39,40].

Conclusion

Based on limited evidence, there seems to be some use of non-TNFα inhibitors in treatment of NIU. Specifically, Tocilizumab has completed randomized control trials that demonstrates significant improvement in visual acuity and reduction in macular edema in NIU patients. Additionally, there are case studies and series that indicate some evidence for the use of Adabacept, Tofacitinib, Baricitinib, Secikinumab, Ustekinumab, Anakinra, Canakinumab and Rituximab in treating uveitis symptoms. Hopefully, more studies, especially randomized clinical trials, can be done to further elucidate their capability in effective treatment of non-infectious uveitis.

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Bibliography

1. McCannel CA., *et al*. "Causes of uveitis in the general practice of ophthalmology". *American Journal of Ophthalmology* 121.1 (1996): 35-46.

2. Chang JH., *et al*. "Acute anterior uveitis and HLA- B27". *Survey of Ophthalmology* 50.4 (2005): 364-388.

3. Wakefield D and Chang JH. "Epidemiology of uveitis". *International Ophthalmology Clinics* 45.2 (2005): 1-13.

4. Ooi KGJ., *et al*. "Cytokines and chemokines in uveitis–Is there a correlation with clinical phenotype?" *Clinical Medicine and Research* 4.4 (2006): 294-309.

5. Paley MA., *et al*. "Tofacitinib for refractory uveitis and scleritis". *American Journal of Ophthalmology Case Reports* 13 (2019): 53-55.

6. Jabs DA and Rosenbaum JT. "Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel". *American Journal of Ophthalmology* 131.5 (2001): 679.

7. Dick AD., *et al*. "Fundamentals of Care for Uveitis International Consensus Group. Guidance on Noncorticosteroid Systemic Immunomodulatory Therapy in Noninfectious Uveitis: Fundamentals Of Care for UveitiS (FOCUS) Initiative". *Ophthalmology* 125.5 (2018): 757-773.

8. R Vavricka S., *et al*. "Biologics for extraintestinal manifestations of IBD". *Current Drug Targets* 15.11 (2014): 1064-1073.

9. Vos AD., *et al*. "Cytokines and uveitis, a review". *Current Eye Research* 11.6 (1992): 581-597.

10. Mercier AE., *et al*. "Efficacy of Anti-TNF-α therapy for the treatment of non-infectious uveitis: a retrospective study of 21 patients". *Ocular Immunology and Inflammation* 26.3 (2018): 477-484.

11. Martel JN., *et al*. "Infliximab and adalimumab for uveitis". *Ocular Immunology and Inflammation* 20.1 (2012): 18-26.

12. Kam KW., *et al*. "Infliximab in the treatment of refractory ocular inflammatory diseases". *The Asia-Pacific Journal of Ophthalmology* 4.1 (2015): 19-24.

13. Kruh JN., *et al*. "Infliximab for the treatment of refractory noninfectious uveitis: a study of 88 patients with long-term follow-up". *Ophthalmology* 121.1 (2014): 358-364.

14. Lopez-Gonzalez R., *et al*. "Treatment of refractory posterior uveitis with infliximab: a 7-year follow-up study". *Scandinavian Journal of Rheumatology* 38.1 (2009): 58-62.

15. Vallet H., *et al*. "Infliximab versus adalimumab in the treatment of refractory inflammatory uveitis: a multicenter study from the French Uveitis Network". *Arthritis and Rheumatology* 68.6 (2016): 1522-1530.

16. Karkhur S., *et al*. "Interleukin-6 inhibition in the management of non-infectious uveitis and beyond". *The Journal of Ophthalmic Inflammation and Infection* 9.1 (2019): 17.

17. Calvo-Río V., *et al*. "Tocilizumab in uveitis refractory to other biologic drugs: a study of 3 cases and a literature review". *Clinical and Experimental Rheumatology* 32.4-84 (2014): S54-57.

18. Leclercq M., *et al*. "Tocilizumab for the treatment of birdshot uveitis that failed interferon alpha and anti-tumor necrosis factor-alpha therapy: two cases report and literature review". *Clinical Rheumatology* 37.3 (2018): 849-853.

19. Mesquida M., *et al*. "Long-term effects of tocilizumab therapy for refractory uveitis-related macular edema". *Ophthalmology* 121.12 (2014): 2380-2386.

20. Sepah YJ., *et al*. "Primary (Month-6) Outcomes of the STOP-Uveitis Study: Evaluating the Safety, Tolerability, and Efficacy of Tocilizumab in Patients With Noninfectious Uveitis". *American Journal of Ophthalmology* 183 (2017): 71-80.

21. Tappeiner C., *et al*. "Abatacept in the treatment of severe, longstanding, and refractory uveitis associated with juvenile idiopathic arthritis". *The Journal of Rheumatology* 42.4 (2015): 706-711.

22. Birolo C., *et al*. "Comparable Efficacy of Abatacept Used as First-line or Second-line Biological Agent for Severe Juvenile Idiopathic Arthritis-related Uveitis". *The Journal of Rheumatology* 43.11 (2016): 2068- 2073.

23. Zulian F., *et al*. "Abatacept for severe anti-tumor necrosis factor alpha refractory juvenile idiopathic arthritis-related uveitis". *Arthritis Care and Research* 62.6 (2010): 821-825.

24. Kaur K., *et al*. "Systematic review of tofacitinib: a new drug for the management of rheumatoid arthritis". *Clinical Therapeutics* 36.7 (2014): 1074-1086.

25. Bing SJ., *et al*. "Tofacitinib inhibits the development of experimental autoimmune uveitis and reduces the proportions of Th1 but not of Th17 cells". *Molecular Vision* 26 (2020): 641-651.

26. Paley MA., *et al*. "Tofacitinib for refractory uveitis and scleritis". *The American Journal of Ophthalmology Case Reports* 13 (2018): 53-55.

27. Miserocchi E., *et al*. "JAK inhibitors in refractory juvenile idiopathic arthritis-associated uveitis". *Clinical Rheumatology* 39.3 (2020): 847-851.

28. Huang JX., *et al*. "Ixekizumab for the treatment of ankylosing spondylitis". *Expert Review of Clinical Immunology* 16.8 (2020): 745-750.

29. Hueber W., *et al*. "Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis". *Science Translational Medicine* 2.52 (2010): 52ra72- 52ra72.

30. Dick AD., *et al*. "Secukinumab in the treatment of noninfectious uveitis: results of three randomized, controlled clinical trials". *Ophthalmology* 120.4 (2013): 777-787.

31. Arepalli S and Rosenbaum JT. "The use of biologics for uveitis associated with spondyloarthritis". *Current Opinion in Rheumatology* 31.4 (2019): 349-354.

32. Pepple KL and Lin P. "Targeting Interleukin-23 in the Treatment of Noninfectious Uveitis". *Ophthalmology* 125.12 (2018): 1977-1983.

33. Baerveldt EM., *et al*. "Successful long-term triple disease control by ustekinumab in a patient with Behcet's disease, psoriasis and hidradenitis suppurativa". *Annals of the Rheumatic Diseases* 72.4 (2013): 626-627.

34. Mugheddu C., *et al*. "Successful ustekinumab treatment of noninfectious uveitis and concomitant severe psoriatic arthritis and plaque psoriasis". *Dermatologic Therapy* 30.5 (2017).

35. Fabiani C., *et al*. "Interleukin (IL)-1 inhibition with anakinra and canakinumab in Behçet's disease-related uveitis: a multicenter retrospective observational study". *Clinical Rheumatology* 36.1 (2017): 191-197.

36. Pijls PA and Gilissen LP. "Vedolizumab is an effective alternative in inflammatory bowel disease patients with anti-TNF-alpha therapy-induced dermatological side effects". *Digestive and Liver Disease* 48.11 (2016): 1391-1393.

37. Fleisher M., *et al*. "Effects of vedolizumab therapy on extraintestinal manifestations in inflammatory bowel disease". *Digestive Diseases and Sciences* 63.4 (2018): 825-833.

38. Miserocchi E., *et al*. "Long-term treatment with rituximab in severe juvenile idiopathic arthritis- associated uveitis". *British Journal of Ophthalmology* 100.6 (2016): 782-786.

39. Tappeiner C., *et al*. "Abatacept in the treatment of severe, longstanding, and refractory uveitis associated with juvenile idiopathic arthritis". *The Journal of Rheumatology* 42.4 (2015): 706-711.

40. Kenawy N., *et al*. "Abatacept: a potential therapy in refractory cases of juvenile idiopathic arthritis- associated uveitis". *Graefe's Archive for Clinical and Experimental Ophthalmology* 249.2 (2011): 297-300.

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