# Tocilizumab in severe and refractory non-infectious uveitis

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**ABSTRACT**

**Objective.** *To report the safety and efficacy of tocilizumab in patients with severe and refractory non-infectious uveitis.*

**Methods.** *Eight consecutive unselected patients with severe and refractory non-infectious uveitis [Birdshot chorioretinopathy (n=1), Behçet disease (n=1) and idiopathic bilateral panuveitis (n=6)] treated with tocilizumab (8mg/kg every 4 weeks intravenously) were included. The primary outcome was the response to treatment, defined by decrease of inflammatory ocular signs.*

**Results.** *Four (50%) patients were of female gender and the median (IQR) age was 41 (31–47) years. The median number of previous immunosupressants was of 5.5 (4–6.7). Seven patients had been previously treated with anti-TNF-α [infliximab (n=5) and adalimumab (n=2)]. The immunosupressive drugs used in association with tocilizumab were azathioprine (n=2), mycophenolate mofetil (n=2) and methotrexate (n=2). After a median follow-up of 8 months (6–25), 6/8 (75%) improved under tocilizumab and 2 (25%) were non-responders. The visual acuity improved in five patients. The median dose of prednisolone decreased from 16mg/day (10.6–20.5) to 10 mg/day (10–13.7), at baseline and at the end of follow-up, respectively. Tolerance of tocilizumab was satisfactory and side effects included bronchitis (n=1) and grade 1 leukopenia (n=1) and thrombocytopenia (n=1).*

**Conclusion.** *Tocilizumab seems to be a safe and promising therapy in severe and refractory non-infectious uveitis.*

Until the late 20th century, the treatment of inflammatory ophthalmologic manifestations of systemic diseases was based on glucocorticosteroids and immunosuppressants in case of corticodependance (1). A better understanding of the mechanisms involved in the inflammatory response and regulation of adaptive immunity led to the development of biotherapeutics (2). Under this term are grouped interferons, intravenous immunoglobulins and monoclonal antibodies. These were mostly developed in the field of rheumatology and then used for the treatment of systemic diseases and inflammatory eye diseases. Several open prospective studies have shown the effectiveness of IFN-α and of anti-TNF-α (infliximab and adalimumab) for the treatment of severe uveitis (3).

Although as yet little used in ophthalmology, tocilizumab, a humanised anti-human IL-6 receptor antibody that inhibits the biological activities of IL-6 by blocking its receptor, could be used in the near future, for the treatment of uveitis. IL-6 is a pleiotropic pro-inflammatory cytokine with multiple functions and secreted by T cells, monocytes, macrophages and synovial fibroblasts, involved in the immune response (induction of differentiation of Th17 cells) hematopoiesis and inflammation. This cytokine also increases vascular permeability and angiogenesis. The receptor for IL-6 is a complex formed of the signal transduction molecule gp130 and the membrane receptor for IL-6. It also exists as a soluble receptor of IL-6 which is released into the blood and inflamed tissues. IL-6 can bind to two receptor types; the IL6/soluble receptor of IL-6 complex can bind to the membrane molecule gp130 and induce signal transduction. Tocilizumab prevents the binding of IL-6 with its membrane and soluble receptors and also antagonises its action. Tocilizumab is used for the treatment of active rheumatoid arthritis, moderate to severe (i) in combination with methotrexate, in case of inadequate response to at least one DMARD or in case of inadequate response or intolerance to at least one anti-TNF (ii) in monotherapy, in case of intolerance

**Table I.** Characteristics of the 8 patients with severe and refractory non-infectious uveitis.

| Case* | Age (years)/ Sex | Eye inflammation | Previous treatments | Follow-up (months) | DMARDs | Initial prednisone dose (mg/day) | Prednisone dose at EOF (mg/day) |
|---|---|---|---|---|---|---|---|
| 1 | 71/F | Birdshot | AZA, IVIg, MMF, ADA | 11 | MMF | 12.5 | 7.5 |
| 2 | 40/M | Idiopathic bilateral panuveitis and retinal vasculitis | AZA | 9 | AZA | 20 | 10 |
| 3 | 28/F | Granulomatous bilateral panuveitis | MTX, AZA, MMF, ADA | 6 | None | 15 | 10 |
| 4 | 42/F | Granulomatous bilateral panuveitis | AZA,MMF, IFNα, MTX, IFX, ADA | 8 | MTX | 30 | 15 |
| 5 | 47/M | AS bilateral macular oedema and panuveitis | MTX, CYC, CysA, ANA, IFX, ADA, ABA | 25 | MTX | 17 | 10 |
| 6 | 40/M | Behçet's bilateral panuveitis and retinal vasculitis | CYC, MMF, IFNα, IFX, ADA | 6 | MMF | 30 | 60 |
| 7 | 48/F | Idiopathic bilateral panuveitis and retinal vasculitis | AZA, MTX, CYC, IFNα, IFX, ADA | 8 | AZA | 10 | 10 |
| 8 | 21/M | Bilateral macular oedema and panuveitis | MTX, AZA, IFX, ADA, ANA, CyA, IFNα | 7 | None | 10 | 10 |

F: female; M: male; AS: associated spondylarthropathy; AZA: azathioprine; IVIg: intravenous immunoglobulins; MMF: mycophenolate mofetil; ADA: adalimumab; IFNα: interferon-α; IFX: infliximab; CYC: cyclophosphamide; CyA: cyclosporine; ANA: anakinra; ABA: abatacept; EOF: end of follow-up.

to methotrexate or when continued treatment is inadequate. More recently a marketing authorisation has been granted for the treatment of active systemic juvenile idiopathic arthritis (JIA) in children aged 2 years and older who have had an inadequate response to treatment with NSAIDs and/or systemic corticosteroids, in combination with methotrexate or in case of intolerance or contraindication to it. Apart from these two pathologies, many retrospective or open studies have shown efficacy of tocilizumab in inflammatory and/or autoimmune diseases refractory to conventional therapy and/or other biologics (4-6). This mostly included series of large vessels vasculitis (Takayasu's arteritis, giant cell arteritis), BD, adult onset Still's disease, multicentric Castleman disease, relapsing polychondritis, Cogan's disease, inflammatory myositis and lupus.

Dysregulated production of IL-6 has been found in several chronic inflammatory disorders, such as rheumatoid arthritis or Behçet's disease. It has been demonstrated that IL-6 is essential, in association with TGF-beta and IL23, for the differentiation of Th17 from naïve $CD4^+$ T cells *in vitro* (7) and that their inhibition leads to auto-immune diseases prevention (8). Experiments in mice suggested that IL6-R blocking antibody might improve ocular inflammation in autoimmune uveoretinitis, by inhibiting Th17 cells development and increasing Treg cells (9-11).

Few cases have been reported on the safety and efficacy of tolicizumab in patients with non-infectious uveitis (12-13) We conducted a preliminary study to assess efficacy and safety of tocilizumab in patients with severe non-infectious uveitis, refractory to immunosuppressants and/or anti-TNF-α.

## Methods

*Patients*

Eight consecutive unselected patients followed at La Pitié-Salpêtrière university Hospital in Paris and Dijon university Hospital, France between 2011 and 2013 were included. We included patients above the age of 18, diagnosed with severe non-infectious and refractory posterior uveitis or panuveitis and/or retinal vasculitis and/or chronic macular oedema. All patients were resistant at least one immunosupressive drug. Tocilizumab was administred intravenously at a dose of 8mg/kg every 4 weeks. The data recorded include age, sex, type of eye inflammation, previous and actual immunosuppressive drug, daily dose of prednisolone, visual acuity and outcome. The primary outcome was the response to treatment, defined by decrease of inflammatory ocular signs. Relapse was defined by any ocular event requiring a change of immunosupressive drug and/or an increased dose of corticosteroids. All the adverse events were recorded. Ophthalmologic examination included measurement of the best-corrected visual acuity (BCVA), tonometry, and slip-lamp examination. Funduscopy was performed to assess vitritis, retinal hemorrhages, vasculitis, papillitis, and retinal ischemia. Fluorescein angiography was performed in all cases. Improvement of uveitis was based on international criteria and was defined as a two step decrease in the level of inflammation or decrease to grade 0 (1). Based on the criteria recently reported by the standardisation of uveitis nomenclature working group, improved activity was defined as a two step decrease in the level of inflammation or decrease to grade 0 (1). Evolution of visual acuity, control of intraocular inflammation (regression of retinal vasculitis) and levels of steroid dependence were evaluated as major criteria for drug efficacy. Loss or gain of visual acuity was evaluated across the 0.4 or worse (visual impairement) and the 1.0 or worse (legal

blindness) thresholds according to the standardisation of uveitis nomenclature working group (1).

*Literature review*

We systematically screened the medical literature via PubMed (http:// www.ncbi.nlm.nih.gov/pubmed) using the following keywords: "Uveitis", and "Tocilizumab". We only analysed cases reports and series published in English.

*Statistical analysis*

Data are summarised as frequencies and percentages for categorical variables. Quantitative variables are presented as medians (Q1;Q3) or mean ± SD.

## Results

*Characteristics of patients*

Main data are summarised in Table I and II. Eight patients with severe and refractory uveitis were enrolled, of whom 50% were of female gender. The median age was 41 (31–47) years. Characteristics of uveitis included Birdshot chorioretinopathy (n=1), idiopathic bilateral panuveitis and retinal vasculitis (n=2), granulomatous bilateral panuveitis (n=2), bilateral macular oedema and panuveitis (n=2) and Behçet disease with retinal vasculitis (n=1). Median visual acuity (VA) before initiation of therapy was 5 [5 (1-10) right eye and 3.2 (0–10) left eye)], with a loss of useful vision at baseline in 4 (50%) patients.

The median number of previous immunosupressants was of 5.5 (4-6.7). Previous immunosupressants included azathioprine (n=8), methotrexate (n=7), mycophenolate mofetil (n=4) and cyclosporine (n=3). Seven patients had been previously treated with anti-TNF-α, [infliximab (n=5) and adalimumab, (n=2)]. The median dose of prednisolone was 16mg/day (10.6-20.5), and the immunosupressive drugs used in association with tocilizumab were azathioprine (n=2), mycophenolate mofetil (n=2) and methotrexate (n=2).

*Efficacy and safety*

After a follow-up of 8 months (6-25), 6/8 (75%) were complete responders (*i.e.* complete control of inflammation) under tocilizumab and 2 (25%) were non-responders (Table II). The visual acuity improved in 4 patients and stabilised in 4 patients. Loss of useful vision was noted in 4 (50%) and 3 (37.5%) cases, respectively at baseline and at the end of follow-up. Among the 6 complete responders, four patients had an improvement of visual acuity, and all of them had a control of inflammatory ocular signs. The median dose of prednisolone at the end of follow-up was 10mg/day (10–13.7). Four patients (50%) exhibited at least one relapse. Tocilizumab was discontinued in 4 patients, because of relapse of uveitis in three cases, and because of severe obesity in a non-infusible patient.

No serious adverse effects were noted. Three side effects were observed, including a non-serious bronchitis treated with one week antibiotherapy, and a grade 1 leukopenia and thrombocytopenia, with no bleeding or infection symptoms. No treatment discontinuation was required because of side effect.

*Review of the literature*

The data are summarised in Table III. Adan *et al*. described five cases of patients with refractory uveitis treated with tocilizumab. All were of female gender and the mean age was 49.4 years (range, 30–68 years). Characteristics of uveitis included Birdshot chorioretinopathy (n=3), juvenile idiopathic arthritis-associated uveitis (n=1), and idiopathic panuveitis (n=1). All patients had been previously treated with anti-TNF-α. Five patients (100%) responded to treatment, with a decrease of Central Foveal Tickness (CVT) measured with optical coherence tomography (OCT).

**Table II.** Outcome of the 8 patients with severe and refractory non-infectious uveitis treated with tocilizumab.

| Case ≠ | Outcome | Visual acuity at baseline (R; L) | Visual acuity at EOF (R; L) | Side effects |
|---|---|---|---|---|
| 1 | Improvement | 0.4; 0.15 | 0.045; 0 | Bronchitis |
| 2 | Improvement | 0; 0 | 0; 0 | - |
| 3 | Improvement | 0.22; 0 | 0.1; 0 | - |
| 4 | Non response | 1.0; 2.0 | 1.0; 2.0 | - |
| 5 | Improvement | 0.22; 1.3 | 0.1; 0.6 | - |
| 6 | Non response | 1.0 ; 2.0 | 1.0; 2.0 | - |
| 7 | Improvement | 0.7; 2.0 | 0.7; 2.0 | - |
| 8 | Improvement | 0.1; 0.22 | 0.1; 0.15 | Leucopenia, thrombocytopenia |

R: right; L: left; EOF: end of follow-up. Visual acuity was expressed as LogMAR.

**Table III.** Review of the litterature of patients treated with tocilizumab for severe and refractory non-infectious uveitis.

| Case≠ | Age (years) /Sex | Eye inflammation | Previous treatments | Follow-up (months) | Prednisone dose (mg/day) | Outcome | Side Effects |
|---|---|---|---|---|---|---|---|
| 1 | 30/F | Juvenile idiopathic arthritis | CyA, ADA, RTX, ABT | 7 | 5 | Improvement | - |
| 2 | 56/F | Idiopathic bilateral panuveitis | CyA, MTX, IFX, ADA | 12 | 5 | Improvement | - |
| 3 | 54/F | Birdshot | CyA, MMF, ADA | 9 | 7,5 | Improvement | - |
| 4 | 68/F | Birdshot | CyA, MMF, ADA | 8 | 7,5 | Improvement | - |
| 5 | 39/F | Birdshot | CyA, IFX, ADA | 6 | 0 | Improvement | - |
| 6 | 47/F | Behçet's bilateral panuveitis | CYC, IFX | 12 | 0 | Improvement | Increase in LDLc |

F: female; M: male; MMF: mycophenolate mofetil; ADA: adalimumab; IFX: infliximab; CYC: cyclophosphamide; CyA: cyclosporine; RTX: rituximab.

Improvement of visual acuity was noted in four patients (80%) and stabilisation was noted in one (20%). After a follow-up of 6 months, sustained remission of uveitis was maintained in all patients and no side effects were reported.

Hirano *et al*. described a case report of a 47-year old female patient treated with tocilizumab for a refractory bilateral uveitis associated with Behçet's disease. She had been treated previously with cyclosporine A and infliximab. With tocilizumab, the frequency and severity of ocular attacks decreased, along with improvement in visual acuity. Occasional administration of low-dose prednisolone (5 to 15 mg/day for 2 days) was required for mild ocular attacks. There were no adverse events, except for a transient increase in the serum low-density lipoprotein (LDL)-cholesterol level.

## Discussion

IL-6 is a cytokine involved in the pathogenesis of experimental autoimmune uveitis. This experimental model immunises rats against the S antigen of the retina or the binding protein of the retinal photoreceptors. Several studies in rats and mice have shown that IL-6 was involved in the genesis of the inflammatory process and the invalidation of the IL-6 gene for IL-6 or the blocking of this molecule by tocilizumab warned the onset of uveitis by the suppression of Th17 response both locally and systemically (14). Haruta *et al*. have recently shown that tocilizumab also increased, in this context, Th1 cells specific regulatory binding protein of retinal photoreceptors (11). These data suggest that blocking the IL-6 monoclonal antibodies could be effective for the treatment of refractory uveitis associated with an inflammatory or autoimmune condition. To date, several case-reports have shown the interest of tocilizumab in the treatment of uveitis refractory to anti-TNF, including idiopathic uveitis, Birdshot's disease (12-13, 15). Tappeiner *et al*. reported the efficacy of tocilizumab in three adult patients with uveitis associated with juvenile idiopathic arthritis refractory to immunosuppressants and anti-TNF (16). An ongoing trial in United States evaluates the efficacy of tocilizumab for the treatment of uveitis in juvenile idiopathic arthritis in case of failure or intolerance of immunosuppressants. More recently, Adan reported the efficacy of tocilizumab in five patients with refractory uvetis-related cystoid macular oedema (15).

The present study reports the largest series of patients treated with tocilizumab for severe uveitis refractory to corticosteroids, immunosuppressive therapy and biological therapy, including anti-TNF antibodies. In our study, all patients had a reccurent, refractory uveitis at baseline, and 75% of them improved their ocular inflammation signs and/or their visual acuity under tocilizumab. It is important to highlight that all patients in this study were refractory to a large number of immunosupressive drugs, including anti-TNF antibodies in all except one case. We also want to point out that the two patients who didn't respond with tocilizumab were the patients with the most severe ocular inflammation at inclusion, with an important loss of visual acuity in both eyes. Tocilizumab acts rapidly to decrease ocular inflammation. However, the relative short-term follow-up of this study could not allow the assessment of long-term remission. Four patients (50%) exhibited at least one relapse under tocilizumab leading to discontinuation of therapy in 3 cases. Our results are in line with with the few cases reported in the literature. Compared with anti-TNF antibodies, tocilizumab has the theorical advantage of being used as monotherapy (*i.e*. without DMARD), as demonstrated in rheumatoid arthritis (17) and juvenile arthritis. However, only two patients in this study received tocilizumab alone, but there were no difference with respect to efficacy compared to those treated with tocilizumab in association with DMARDs. Interestingly, the dose of corticosteroids used in association to tocilizumab was low and did not exceed 30mg/day.

No serious adverse effects were noted in our patients or in the litterature. The main side effects of tocilizumab reported in the literature included upper respiratory tract infection (most common), increased transaminases level, hypertension, headache, dizziness, and nasopharyngitis. In the present study, two patients (25%) experienced an adverse event including one bronchitis, and a grade 1 leukopenia and thrombocytopenia. No treatment discontinuation was required because of side effect.

We acknowledge some limitations of the current study. Our analysis was retrospective with a relatively small number of patients and a short follow-up period. Long-term effects of tocilizumab remain unknown. Prospective controlled trials are underway to assess the therapeutic benefit of IL-6 inhibitors in patients with severe uveitis. In conclusion, tocilizumab seems to be a safe and promising therapy in severe and refractory non-infectious uveitis. These results suggest that IL-6 may play an important pathogenic role in non-infectious uveitis.

## References


1. JABS DA, ROSENBAUM JT: Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol* 2001; 131: 679.
2. CAORSI R, FEDERICI S, GATTORNO M: Biologic drugs in autoinflammatory syndromes. *Autoimmun Rev* 2012; 12: 81-6.
3. SAADOUN D, BODAGHI B, BIENVENU B *et al*.: Biotherapies in inflammatory ocular disorders: Interferons, immunoglobulins, monoclonal antibodies. *Autoimmun Rev* 2013; 12: 774-83.
4. KALY L, ROSNER I: Tocilizumab - a novel therapy for non-organ-specific autoimmune diseases. *Best Pract Res Clin Rheumatol* 2012; 26: 157-65.
5. PAZZOLA G, PADOVANO I, BOIARDI L *et al*.: Tocilizumab in glucocorticoid-naïve large-vessel vasculitis. *Clin Exp Rheumatol* 2013; 31 (Suppl. 75): S59-61.
6. BENUCCI M, MANFREDI M, SAVIOLA G, SARZI-PUTTINI P, ATZENI F: Changes in atherosclerosis markers during tocilizumab treatment in rheumatoid arthritis: preliminary results. *Clin Exp Rheumatol* 2013; 31: 322-3.
7. KIMURA A, NAKA T, KISHIMOTO T: IL-6-dependent and –independent pathways in the development of interleukin 17-producing T helper cells. *Proc Natl Acad Sci USA* 2007; 104: 12099-104.
8. MIHARA M, OHSUGI Y, KISHIMOTO T: Evidence for the role of Th17 cell inhibition in the prevention of autoimmune diseases by anti-interleukine-6 receptor antibody. *Biofactors* 2009; 35: 47-51.
9. YOSHIMURA T, SONODA KH, OHGURO N *et al*.: Involvement of Th17 cells and the effect of anti-IL-6 therapy in autoimmune uveitis, *Rheumatology* (Oxford) 2009; 48: 347-54.

10. HOHKI S, OHGURO N, HARUTA H *et al*.: Blockade of interleukin 6 signaling suppresses experimental auto-immune uveoretinitis by the inhibition of inflammatory Th17 responses, *Exp Eye Res* 2010; 91: 162-70.
11. HARUTA H, OHGURO N, FUJIMOTO M *et al*.: Blockade of Interleukin-6 signaling supresses not only Th17 but also interphotoreceptor retinoid binding protein-specific Th1 by promoting Regulatory T Cells in experimental autoimmune uveoretinitis. *Invest Ophthalmol Vis Sci* 2011; 52: 3264-71.
12. MUSELIER A, BIELEFELD P, BIDOT S, VINIT J, BESANCENOT JF, BRON A: Efficacy of tocilizumab in two patients with anti-TNF-alpha refractory uveitis. *Ocul Immunol Inflamm* 2011; 19: 382-3.
13. HIRANO T, OHGURO N, HOHKI S *et al*.: A case of Behçet's disease treated with a humanized anti-interleukin-6 receptor antibody, tocilizumab. *Mod Rheumatol* 2012; 22: 298-302.
14. YOSHIMURA T, SONODA KH, OHGURO N *et al*.: Involvement of Th17 cells and the effect of anti-IL-6 therapy in autoimmune uveitis. *Rheumatology* (Oxford). 2009; 48: 347-54.
15. ADÁN A, MESQUIDA M, LLORENÇ V *et al*.: Tocilizumab treatment for refractory uveitis-related cystoid macular edema. *Graefes Arch Clin Exp Ophthalmol* 2013; 251: 2627-32.
16. TAPPEINER C, HEINZ C, GANSER G, HEILIGENHAUS A: Is tocilizumab an effective option for treatment of refractory uveitis associated with juvenile idiopathic arthritis? *J Rheumatol* 2012; 39: 1294-5.
17. JONES G, SEBBA A, GU J *et al*.: Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis* 2010; 69: 88-96.