

When eye is involved is the management different? Eye treatment protocol

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Immunomodulatory therapy

- Conventional (Anti metabolites, Anti T cells, Alkylating Agents)
- Biologic Response Modifiers (Adalimumab, Rituximab, Infliximab, Interferon, Tocilizumab)



Orphan Drugs

Approved orphan drugs by the US Food and Drug Administration to be in systemic diseases and/or organ transplantation while not received “orphan drug approval” to be used in uveitis (II) – mechanism and using

Medication	Mechanism of action	Dosage/route	Potential side effects
Methotrexate	Antimetabolites/inhibits dihydrate folate reductase	7.5–25 mg per week given with folic acid, p.o., S.C.	Gastrointestinal disturbance, hepatotoxicity, oral ulcers, fatigue, alopecia, bone marrow suppression, pneumonitis, fetal loss, and infections
Tacrolimus	T-cell inhibitor/calcineurin inhibitor	0.1–0.15 mg/kg/day, p.o.	Nephrotoxicity, hypertension, diabetes mellitus, electrolyte imbalance, and infections
Infliximab	Anti-TNF α	3–5 mg/kg loading at weeks 0, 2, and 6, then maintenance 3–10 mg/kg every 4–8 weeks; maximal dose 20 mg/kg in children, I.V.	Susceptibility to infections, including reactivation of tuberculosis, histoplasmosis, hepatitis B, and fungal infection; hypersensitivity reactions; demyelinating disease; lupus-like syndrome; malignancy; thromboembolic events; congestive heart failure
Interferon α -2a	Biologic/antiimmunomodulatory effects	3–9 million units once daily to three times weekly, S.C.	Injection-site reaction, flu-like syndrome, fatigue, depression, neutropenia, elevation of liver enzymes, and rarely INF α -2a retinopathy
Rituximab	Biologic/anti-CD20	1,000 mg or 375 mg/m ² given twice at 2-week intervals, I.V.	Susceptibility to infections, infusion reactions, gastrointestinal disturbance, cardiovascular events, muscle spasm, and headache and multifocal leukoencephalopathy
Tocilizumab	Cytokine receptor antibodies/anti-IL-6 receptor	Initial 4 mg/kg every 4 weeks then increase to 8–12 mg/kg every 2–4 weeks, I.V.	Serious infections, hypersensitivity reactions, hypercholesterolemia, and gastrointestinal perforation
Anakinra	Cytokine receptor antibodies/anti-IL1 receptor	100 mg daily, S.C.	Injection-site reaction, infections, headache, gastrointestinal disturbance, and fever
Canakinumab	Monoclonal antibody against IL-1 β	Systemic juvenile idiopathic arthritis: 4 mg/kg (max 300 mg) S.C. every 4 weeks; cryopyrin-associated periodic syndromes, 2–3 mg/kg SQ every 8 weeks, I.V., S.C.	Susceptibility to infections, headache, nausea, and abdominal pain
Alemtuzumab	Monoclonal antibody against CD52	30 mg I.V., 3 days per week for 12 weeks, I.V.	Cytopenias, infusion reactions, infections, gastrointestinal disturbance, and insomnia

Many types of autoimmune-mediated uveitis are associated with systemic autoimmune diseases and thus the same guidelines can be followed in terms of employing biologic response modifier agents. However, **most uveitis specialists believe that uveitis, whether or not it is associated with a systemic disease, is more stubborn** to immunomodulatory therapy indicating more aggressive treatment with **higher doses** or **shorter intervals** of medications including biologic response modifiers



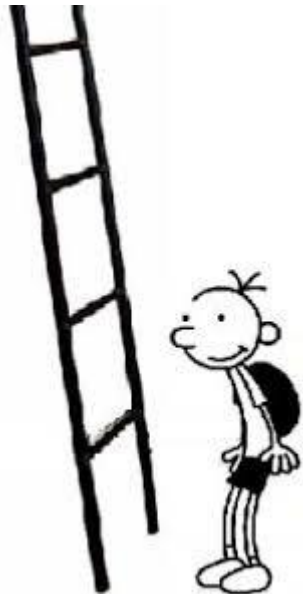
- the paucity of randomized controlled clinical trials, rarity and heterogeneity of uveitis, and high cost of biologic agents make using of them more challenging in the field of ophthalmology especially as the first line of treatment.

- Conventional IMT agents are **the first steroid-sparing options** for uveitic patients with refractive active inflammation and/or sight-threatening complications
- more or less the same, we use more combined medication (Behcet's disease)

- Uveitis is **the third leading cause of legal blindness** in the developed countries.
- Given the side effects of steroids and better understanding of the mechanisms of autoimmune-mediated uveitis, the aim of treatment for patients with autoimmune mediated uveitis is **steroid-free remission** that may be accomplished through the use of immunomodulatory therapy.
- **Immunomodulatory therapy is continued for a period of two years while the patient is in remission before considering tapering the medication.**
- Uveitis, a curable disease in many instances, considered to be cured when there is no recurrence for five years after stopping the treatment.

A stepladder approach

- non-steroidal anti-inflammatory drugs (NSAIDs)
- conventional immunomodulatory agents
- biologic response modifiers.



Although the stepladder approach is most often followed in the treatment of uveitis, sometimes it is reasonable to consider the biologic response modifiers as the first line of treatment in more aggressive forms of immune mediated uveitis such as Behcet's disease uveitis, uveitis associated with retinal vasculitis, uveitis associated with granulomatosis associated with polyangiitis (Wegener's granulomatosis). It should also be considered that failure of a biologic response modifier in a group does not necessarily mean that the similar agents in the same group will also be ineffective.[15] Moreover, some studies show agents in the same group can be replaced with each other from more aggressive treatment such as infusions to less aggressive one such as subcutaneous injections.

Infliximab in uveitis

- Most uveitis specialists believe that eye inflammation **needs more aggressive therapy and a higher dose of infliximab than rheumatological and gastrointestinal problems.** The usual dose is 5-10 mg/kg when used for the treatment of uveitis. However, higher doses of 10-20 mg/kg have been used with success and minimal side effects in patients with chronic uveitis.[10]

Interval for infliximab Q 8 weeks (rheumatology)

Table 2

Statements from guidelines and consensus statements for different auto-inflammatory disorders on issues related to the use of infliximab: dosage regimen, induction therapy, loss of response, loss of response and the use of concomitant medication

Indication	Study, year (reference)	Dosage (mg kg ⁻¹)	Induction therapy (weeks)	Maintenance intervals (in weeks)	Determination of (non) response ⁺	Advice regarding loss of response in patients who initially responded to IFX	Recommended co-medication
CD	Centocor, 2009 [61]	5	0,2,6	8	Active Crohn's disease: after two doses Fistulizing disease: after three doses	Some patients may regain response with dose escalation.	NA
	ECCO, 2006 [6]	5	NA	8	NA	Most try increasing the dose to 10 mg kg ⁻¹	AZA, MP or MTX
	AGA, 2007 [4]	5	0,2,6	8	After two doses	Patients who have attenuated response may be given - higher dose infusions up to 10 mg kg ⁻¹ at 8-week intervals, or - 5 mg kg ⁻¹ at shortened intervals as frequently as every 4 weeks.	Initiated in advance of biologic therapy
	Hommes <i>et al.</i> , 2006 [7]	5	0,2,6	8	4 weeks after the second infusion	Increase to 10 mg kg ⁻¹ on strict verified indication.	Use of an immunosuppressant.
	Panaccione <i>et al.</i> , 2004 [8]	5	0,2,6	8	After three doses	Dosage increasement to 10 mg kg ⁻¹ or shortening of infusion intervals	Concomitant immunosuppressive therapy (eg, 6-MP, AZA or MTX)
UC	Centocor, 2009 [61]	5	0,2,6	8	After three doses	NA	NA
	AGA, 2007 [4] ^{***}						
RA	Centocor, 2009 [61]	3	0,2,6	8	12 weeks	Options: - Increase the dose step-wise by approximately 1.5 mg kg ⁻¹ , up to a maximum of 7.5 mg kg ⁻¹ every 8 weeks <i>or</i> - Administration of 3 mg kg ⁻¹ as often as every 4 weeks may be considered.	MTX
	Furst <i>et al.</i> , 2008 [9]	NA	NA	NA	Within 12-24 weeks	Increasing the dose or reducing the dosing intervals may provide additional benefit in RA, as may the addition or substitution of other DMARDs.	MTX

FDA-Approved Indications and Dosing

- Rheumatoid Arthritis: 3 mg/kg IV at 0, 2 and 6 weeks, then **every 8 weeks**, in conjunction with methotrexate. Some patients may benefit from doses up to 10 mg/kg or treating as often as every 4 weeks.
- Ankylosing Spondylitis: 5 mg/kg IV at 0, 2 and 6 weeks, then **every 8 weeks**.
- Psoriatic Arthritis and Plaque Psoriasis: 5 mg/kg IV at 0, 2 and 6 weeks, then every 8 weeks.
- Crohn's Disease: 5 mg/kg IV at 0, 2 and 6 weeks, then **every 8 weeks**. Some adult patients may benefit from doses up to 10 mg/kg. Approved for use in pediatric patients, 6 years and older.
- Ulcerative Colitis: 5 mg/kg IV at 0, 2 and 6 weeks, then **every 8 weeks**. Approved for use in pediatric patients, 6 years and older.

Impact of different infliximab dose regimens on treatment response and drug survival in 462 patients with psoriatic arthritis: results from the nationwide registries DANBIO and ICEBIO.

Glintborg B¹, Gudbjornsson B¹, Krogh NS², Omerovic E², Manilo N², Holland-Fischer M², Lindegaard HM², Loft AG², Nordin H², Johnsen L², Oeftiger SF², Hansen A², Rasmussen C², Grondal G², Geirsson AJ², Hetland ML¹.

⊕ Author information

Abstract

OBJECTIVE: The aim of this study was to describe dose regimens, dose escalation and clinical outcomes in TNF- α inhibitor (TNFi)-naive patients with PsA treated with infliximab in routine rheumatology care.

METHODS: We conducted an observational cohort study based on the nationwide Danish Rheumatologic Database (DANBIO) and Center for Rheumatology Research (ICEBIO) registries. Stratified by country, characteristics of patients treated with ≤ 3 mg infliximab/kg body weight, 3-5 mg/kg or ≥ 5 mg/kg every 8 weeks were described. Outcomes were evaluated by ACR 20%, 50% and 70% (ACR20/50/70) responses and European League Against Rheumatism good response after 6 months, disease activity after 12 months, Kaplan-Meier plots and regression analyses.

RESULTS: Four hundred and sixty-two patients (376 Danish, 86 Icelandic) received treatment with infliximab. In Danish patients, the starting dose was ≤ 3 mg/kg in 110 patients (29%), 3-5 mg/kg in 157 (42%), ≥ 5 mg/kg in 38 (10%) and unregistered in 71 (19%). In Icelandic patients, corresponding numbers were 64 (74%), 17 (27%), 0 (0%) and 5 (6%). Patients with a higher body weight received lower doses per kilogram. Danish patients received higher doses than Icelandic patients at baseline [median 3.1 (interquartile range 3.0-3.8) vs 2.3 (2.1-2.9) mg/kg, $P < 0.05$] and after 12 months [3.3 (3.0-4.5) vs 2.9 (2.2-3.5) mg/kg, $P < 0.0001$]. After 12 months, 58% of Danish and 66% of Icelandic patients maintained treatment. Danish patients had shorter drug survival than Icelandic patients (1183 vs 483 days). In univariate analyses stratified by country, time until dose escalation, response rates, drug survival and 1-year's disease activity were independent of starting dose. Drug survival was shorter among patients not receiving concomitant MTX.

CONCLUSION: In clinical practice, $> 70\%$ of Icelandic and Danish PsA patients treated with infliximab received sustained doses below the 5 mg/kg every 8 weeks recommended in international guidelines. Lower starting doses did not affect drug survival or response.

The Effectiveness of Pre- and Postoperative Infliximab in Controlling Behçet's Disease Posterior Uveitis in Patients Undergoing Vitrectomy: A Preliminary Study

- Infliximab was given in a dose of 5 mg/kg intravenous infusion once **every two weeks for 3 treatment sessions** before the intended vitrectomy followed by 3 treatment sessions at two-week intervals, after vitrectomy.

Eye Protocol of infliximab

- Infliximab starts at a dose of 5 mg/kg. There were 2 induction doses 2 weeks apart and monthly thereafter for 6 months. Based on the clinical response and ancillary test findings such as FA and OCT findings, the dose was adjusted to a maximum of 10 mg/kg. After 6 months, the interval between doses was lengthened by 1 week after every 4 infusions, and it was stopped when the patient reached 4 doses at an interval of 12 weeks

The activity of arthritis and uveitis are commonly independent

- There should be close relationship between rheumatologist and ophthalmologist for making decision on cessation or tapering medication





Rituximab

- Rheumatology protocol (two doses of 1000mg separated by 14 days, cycled every 3-6 months)
- Lymphoma protocol (375mg/m² weekly x4)
- Eye protocol!(375mg/m² weekly x8 followed by monthly with extension as tolerated for ocular inflammatory disease)→ for scleritis, PUK (GPA, MPA), OCP

Ophthalmology 2010

Combination of rituximab and intravenous immunoglobulin for recalcitrant ocular cicatricial pemphigoid:
a preliminary report. [Foster CS¹](#), [Chang PY](#), [Ahmed AR](#).

Rituximab in the Treatment of Refractory Noninfectious Scleritis.

Cao JH¹, Oray M², Cocho L¹, Foster CS³.

⊕ Author information

Abstract

PURPOSE: To describe the outcomes of the use of rituximab in the treatment of refractory noninfectious scleritis.

DESIGN: Retrospective case series.

METHODS: Review of the medical charts of patients with noninfectious scleritis refractory to conventional immunomodulatory therapy who were seen at the Massachusetts Eye Research and Surgery Institution between 2005 and 2015. The primary outcome measure in this study was steroid-free remission. Secondary outcomes were favorable response (decrease in scleritis activity score) and decrease in steroid dependence.

RESULTS: There were 15 patients, with a mean follow-up duration of 34 months. Fourteen patients (93.3%) showed a clinical improvement, with 13 (86.6%) achieving a scleritis activity score of zero at 6 months. To date, 2 patients continue to enjoy durable drug-free remission (28 and 32 months follow-up). There was only 1 adverse effect recorded (infusion hypotension) requiring cessation of rituximab.

CONCLUSION: Rituximab can be an effective treatment modality for recalcitrant noninfectious scleritis and, in some, can result in long-term durable drug-free remission.

Combination of rituximab and intravenous immunoglobulin for recalcitrant ocular cicatricial pemphigoid: a preliminary report.

Foster CS¹, Chang PY, Ahmed AR.

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Abstract

PURPOSE: To compare the effectiveness and safety of the combination therapy of rituximab (RTX) and intravenous immunoglobulin (IVIg) to other immunosuppressive regimens in the treatment of ocular cicatricial pemphigoid (OCP).

DESIGN: Retrospective, comparative, interventional case series.

PARTICIPANTS: Twelve patients with OCP.

METHODS: We reviewed medical records of 12 patients with OCP. Ten of the 12 patients were blind in 1 eye after initial systemic immunosuppressive therapies (phase 1 treatment). The patients were then divided into 2 groups based on treatments received during phase 2. The study group consisted of 6 patients who received the combination of RTX and IVIg during phase 2 of their treatment. For comparison purposes, the control group consisted of 6 patients who during phase 2 of their treatment received more aggressive immunosuppressive therapies, but not RTX and IVIg, because the insurance carriers refused to pay for the combination therapy.

MAIN OUTCOME MEASURES: Blindness (best-corrected visual acuity [BCVA] < or =20/200) and OCP staging (Foster).

RESULTS: The median total follow-up periods were 57.5 and 55.5 months in the control group and the study group, respectively. After phase 1 treatment, all 6 patients in the control group were blind in 1 eye. Similarly, 4 of the patients in the study group were blind in 1 eye, whereas 2 had good BCVA bilaterally but experienced persistent conjunctival inflammation despite phase 1 treatment. After phase 2 treatment, all 6 patients in the control group had OCP progression and became blind in both eyes. In contrast, BCVA was stable and no further progression of OCP staging was observed in all 6 patients in the study group. In the study group, the median follow-up from completion of the RTX and IVIg treatment protocol was 11 months. No adverse events, immediate or delayed, were reported in any of the patients who received the combination therapy of RTX and IVIg.

CONCLUSIONS: In this preliminary study, the combination therapy of RTX and IVIg arrested disease progression and prevented total blindness in patients with recalcitrant OCP.

- Rituximab Therapy. The dose of RTX was 375 mg/m² and was given **once weekly for 8 consecutive weeks**. Thereafter, for the subsequent 4 months, it was given **once monthly**. Hence, **the patients received 12 infusions over 6 months**. Before RTX, the patients had a detailed medical workup to determine that there was no contraindication to RTX. Among these were computed tomography scans of the neck, chest, and pelvis to exclude preexisting lymphoma or other malignancies.
- Intravenous Immunoglobulin Therapy. Patients were given 1 cycle of IVIg before the initiation of RTX. The **dose of IVIg was 2 g/kg per cycle. The total dose was divided into 3 equal parts on 3 consecutive days**. The frequency of the IVIg was monthly until the B-cell level returned to normal. Thereafter, IVIg was continued and the intervals between infusions were increased to 6, 8, 10, 12, 14, and 16 weeks. The last cycle was given at the 16-week interval. This was considered the end point of the therapy. The IVIg was given to the patients in accordance with a published protocol developed by a consensus development group



Tocilizumab

- (Actemra[®], Genentech, Inc., South San Francisco, CA, USA) is a monoclonal antibody against IL-6 receptors. It has been approved for the treatment of moderate to severe rheumatoid arthritis and polyarticular and systemic JIA refractory to other biologic response modifiers. Studied dosing in adults includes 4 or 8 mg/kg intravenous every 4 weeks for 6 doses. The dosage employed in systemic and polyarticular JIA is 8-12mg/kg and 8- 10mg/kg every 2 weeks, respectively.

Tocilizumab

- In a study conducted by Papo et al., 6 out of 8 patients with refractory noninfectious uveitis including Behcet's disease, BSRC, and idiopathic panuveitis **responded to 8 mg/kg intravenous tocilizumab every 4 weeks.**[97] They also reported relapse of macular edema within three months of stopping treatment.[96]

- Anakinra (Kineret[®], Swedish Orphan Biovitrum AB, Stockholm, Sweden) is a recombinant human naturally occurring IL-1 receptor antagonist (IL-1RA). It is administered **subcutaneously 100 mg daily in adults**

- Canakinumab (Ilaris[®], Novartis Pharmaceuticals Corporation, Basel, Switzerland), the human immunoglobulin G1 (IgG1) anti-IL-1 β monoclonal antibody, is indicated for systemic JIA and cryopyrin-associated periodic syndrome in adults and children 4 years or older. It is administered **subcutaneously or intravenously every 4-8 weeks**. Its effectiveness was demonstrated in a refractory case of Behcet's syndrome associated uveitis with a **150 mg single infusion**

Interferon alpha

- INF- α is employed subcutaneously with a **daily dose of 6 mU daily with tapering to low dose of 3 mU, two or three times a week**. INF- α has been primarily studied in patients with Behcet's disease.[36,111]
- It has also been reported in the treatment of sympathetic ophthalmia, VKH, BSRC, intermediate uveitis, and idiopathic panuveitis.[36,112]
- In a prospective study on patients with sight threatening uveitis, 83% of patients showed a favorable response with subcutaneous daily use of human INF- α 2b.[35]
- INF- α 2b has been found to be an effective option in the treatment of refractory CME secondary to uveitis.[113]
- INF- β also has been successfully employed in the treatment of intermediate uveitis associated with multiple sclerosis, choroiditis, and choroidal neovascularization in chronic recurrent punctate inner choroidopathy.[114,115] Interferon therapy can cause severe adverse effects including sarcoidosis with or without uveitis.[116,117] Thus it is not recommended in the treatment of sarcoid-related uveitis.

Interferon alpha benefits

- Tuberculosis
- Anti viral effects
- Multiple sclerosis
- Low price

Many are off label yet

- Adalimumab has FDA approval

Adalimumab

- Ankylosing spondylitis: SubQ: 40 mg every other week (may continue methotrexate, other nonbiologic DMARDs, corticosteroids, NSAIDs and/or analgesics)
- Crohn disease: SubQ (may continue aminosalicylates and/or corticosteroids; if necessary, azathioprine, mercaptopurine, or methotrexate may also be continued):
 - **Initial: 160 mg** (given as four 40 mg injections on day 1 or given as two 40 mg injections per day over 2 consecutive days), then 80 mg 2 weeks later (day 15).
 - Maintenance: 40 mg every other week beginning day 29. Note: Some patients may require 40 mg every week as maintenance therapy (Lichtenstein 2009).

- Psoriatic arthritis: SubQ: 40 mg every other week (may continue methotrexate, other nonbiologic DMARDs, corticosteroids, NSAIDs and/or analgesics) Pyoderma gangrenosum (of-label use): SubQ: 40 to 80 mg every week or every other week (Fonder 2006; Hefernan 2007; Hubbard 2005; Jacob 2008). Additional data may be necessary to further define the role of adalimumab in the treatment of this condition.
- Rheumatoid arthritis: SubQ: 40 mg every other week (may continue methotrexate, other nonbiologic DMARDs, corticosteroids, NSAIDs, and/or analgesics); patients not taking concomitant methotrexate may increase dose to 40 mg every week
- **Ulcerative colitis:** SubQ (may continue aminosalicylates and/or corticosteroids; if necessary, azathioprine, or mercaptopurine may also be continued):
 - Initial: **160 mg** (given as four 40 mg injections on day 1 or given as two 40 mg injections per day over 2 consecutive days), then 80 mg 2 weeks later (day 15).
 - Maintenance: 40 mg every other week beginning day 29. Note: Only continue maintenance dose in patients demonstrating clinical remission by 8 weeks (day 57) of therapy.

Adalimumab for Uveitis

- Initial: 80 mg as a single dose
- Maintenance: 40 mg every other week beginning 1 week after initial dose

Alkylating agent

- The white blood cell (WBC) count guides the dosing of cytotoxic agents. Daily use of these drugs appears to be more effective than pulse therapy in the treatment of uveitis. The goal is to escalate the dose until the WBC is 3000 to 4000 cells/ μ l

Rheumatologic drugs not effective for eye inflammation

- Etanercept
- sulfasalazine

Name:

Date:

Sings of Behcet's disease activity

1- Ant. chamber cells (indicative of iridocyclitis) in the wide beam with a 1×1mm narrow slit.

	OD	OS
0- < 1 <u>cell</u> < 6-15 cells/field : 0 point	☐	☐
1+ = 6-15 cells / field : 1 point	☐	☐
2+ = 16-25 cells / field : 2 point	☐	☐
3+ = <u>26-50</u> cells / field : 3 point	☐	☐
4+ = <u>≥ 51</u> cells / field : 4 point	☐	☐

2-Vitreous haze

	OD	OS
4+ <u>Optic</u> disc is obscure : 4 point	☐	☐
3+ <u>Optic</u> disc can be seen but borders are quite blurry : 3 point	☐	☐
2+ <u>Optic</u> visualization of retinal vessels : 2 point	☐	☐
1+ <u>Optic</u> definition of optic nerve head & retinal vessels : 1 point	☐	☐
<u>Optic</u> - 0) slight blurring of optic disc margin & reflex of the NTL cannot be visualized -- no haze : 0 point	☐	☐

2- Retinal inflammatory changes in periphery including:

ischemia (capillary nonperfusion) or vascular accident or leakage or vasculitis or retinitis or edema exudates or hemorrhage

exudates of each quadrant : 2 points



OD OS Points

3- Retinal inflammatory changes in the fovea

edema (evaluated by OCT) or hemorrhage, exudates, patch of retinitis (in exam) or ischemia, vasculitis, leakage (evaluated by FA) (ischemia, vasculitis, leakage (evaluated by FA))



	OD	OS
<1 disc : 1 point	☐	☐
≥ 1 disc < 2 disc : 2 point	☐	☐
≥ 2 disc < 3 disc : 4 point	☐	☐
≥ 3 disc : 6 point	☐	☐

4-Inflammatory changes in the optic disc and within 2 disc diameter (excluding the temporal side of the optic disc)

Edema (hyperemia and leakage) or new vessel or hemorrhage or exudate : 2point



Presence of inflammation of other ocular structures: adentia, conjunctivitis, corneal ulcer....

OD OS points



**Thank
You!!!**