

## Treatment of Uncontrolled Anterior Uveitis with 5- Fluorouracil: Case Series

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**Abstract:** A case series of six patients with uncontrolled anterior uveitis of different etiology were treated with subconjunctival injections of 5-Fluorouracil (5-FU 5.0 mg/0.1 ml with a total dose of 15-20 mg over 2-3 weeks. All patients showed complete remission of anterior uveitis and control of uveitic glaucoma for  $\geq 9$  months. 5-Fluorouracil might be an effective alternative to corticosteroids in controlling anterior uveitis. Patients at high risk of corticosteroids complications and those with uveitic glaucoma may benefit from this drug.

**Key words:** Anterior uveitis, Glaucoma, Endophthalmitis, 5-Fluorouracil

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### Introduction

Anterior uveitis is a group of inflammatory disorders characterized by inflammation of the iris and ciliary body. In most cases it is difficult to control and associated with serious complications which can be related to the disease itself or its medications. There are many agents that can be used to treat anterior uveitis which include corticosteroids, nonsteroidal anti-inflammatory agents, and immunosuppressive agents.<sup>[1]</sup> 5-Fluorouracil (5-FU) is known as a useful adjunct to filtering surgery in eyes at high risk of operative failure<sup>[2]</sup>. Foster & Vitale<sup>[1]</sup> noticed that using 5-FU injections postoperatively in a patient having combined trabeculectomy and extra capsular cataract extraction improved the survival of trabeculectomy and markedly reduced the severity and duration of the post - operative inflammation. Similar observation has been reported earlier by Walsh et al<sup>[3]</sup>. Ophir and Ticho reported complete remission of anterior uveitis in patients with uveitic glaucoma who had filtering surgery and 5-FU injections post-operatively<sup>[4], [5]</sup>. In this case series we report our experience of using 5-FU in the treatment of different types of anterior uveitis.

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### **Case 1**

A 20-year-old female was referred to our glaucoma clinic with the diagnosis of right idiopathic anterior uveitis and uncontrolled intraocular pressure (IOP) on maximum tolerated medical treatment. The patient was diagnosed to have right idiopathic anterior uveitis five years ago and put on topical steroid. Two years ago, she developed uveitic glaucoma which was responding to topical anti-glaucoma medications. For the last 6-months her IOP became resistant to topical and systemic anti-glaucoma medications and she was advised to have trabeculectomy. On examination, her best corrected visual acuity was 20/200 OD and 20/20 OS. Right pupil showed relative afferent pupillary defect (RAPD). Slit lamp (SL) examination of the right eye showed mild conjunctival congestion, mild corneal edema, deep anterior chamber (AC) with 2+ cells and flare and normal iris and lens. The IOP was 36 mmHg OD and 10 mmHg OS. Gonioscopy of both eyes revealed open angle grade IV 360° (Shaffer's classification). Fundus examination of the right eye showed cup/disc ratio of 0.9 with normal vitreous and retina. The patient was on the following drops, Pred - forte (Prednisolone Acetate) qid, Alphagan (Brimonidine) tid, Betagan (Levobunolol) bid, Trusopt (Dorzolamide HCl) tid and Diamox (Acetazolamide) 250 mg tablet qid. She was not keen to have filtering operation. The possibility of steroid responder behind uncontrolled IOP was discussed with the patient and she was offered to receive 5-FU subconjunctival injections instead of steroid. Pred - forte was discontinued and she was given 5 mg/0.1ml of 5-FU subconjunctival injection in the inferior fornix, and she was kept on all anti-glaucoma medications. 2 days later she was seen, and the AC reaction decreased to 1+ cell and IOP dropped to 30 mmHg.

The patient was given a second injection of 5-FU. One week later her vision improved to 20/60, with white conjunctiva, clear cornea, occasional cells in AC, and IOP 20 mmHg. She was given a third injection of 5-FU. 3 weeks later her vision improved to 20/40, with quiet AC, and IOP dropped to 16 mmHg. The patient continued to have quiet AC and normal IOP in the low teens over the following two months and all anti-glaucoma medications could be stopped except Betagan. No recurrence of uveitis or increase of IOP was noted in the last three years.

### **Case 2**

A 42 year old female presented to the glaucoma clinic on the 24<sup>th</sup> of November 2001 complaining of pain and redness in the right eye for three weeks. She was seen in the government eye hospital and diagnosed to have right anterior uveitis with secondary pupillary block glaucoma. She had YAG laser peripheral iridectomy (PI) and put on Cosopt (Dorzolamide/Timolol maleate) eye drops tid, Alphagan eye drops tid, Vexol (Rimexolone) eye drops Qid and Diamox 250 mgt tablets qid. On examination her best corrected vision, OD 0.7 and OS 1.0. SL examination of the right eye revealed congestion of conjunctiva, clear cornea, shallow AC grade (I) (Shaffer's classification) with 1+ cell and flare, 360° posterior synechiae with iris bombe and occluded PI at 12 o'clock. IOP was 50 mmHg OD and 10 mmHg OS. Gonioscopy of of the right eye revealed closed angle grade (0) 360° and open angle grade (IV) in OS.

All investigations excluded the possibility of uveitis. She was put on oral prednisolone 20 mg/day with maximum tolerated anti glaucoma medications and underwent right trabeculectomy with Mitomycin – C (MM-C) 0.2mg/ml for 4 minutes. Post-operatively, the patient continued to have significant inflammation with creeping up of IOP in spite of systemic and topical steroids. The patient was given four injections of 5-FU 5mg/0.1ml subconjunctival in the inferior fornix over two weeks and had Argon laser suturlysis. She continued to have quiet eye and normal IOP without medications for two years.

### **Case 3**

A 78 year old male patient, who had on the 2<sup>nd</sup> of February 2002 uncomplicated left extra capsular cataract extraction and posterior chamber intra-ocular lens (IOL) implantation. Postoperative course was routine and uneventful. On 26<sup>th</sup> of March 2002, he came to the clinic complaining of pain and floaters for two days after he discontinued Maxitrol (Dexamethasone, Neomycin, Polymyxin B sulphate) drop and ointment. Examination of the left eye showed best corrected vision of 20/60, SL examination showed congestion of conjunctiva, clear cornea, with deep AC full of cells and presence of hypopyon. IOP was 15 mm Hg. Gonioscopy revealed grade IV open angle. On dilating the pupil, fluffy white material (plaque) could be seen behind the IOL on the nasal side and the retina could be examined easily with the indirect ophthalmoscope in spite of 1+ cell in the anterior vitreous. The patient was diagnosed to have severe uveitis secondary to cortical material or questionable sterile endophthalmitis. He was admitted to hospital and received endophthalmitis treatment regimen in form of fortified drops of Gentamycin 13mg/ml, and Cefazolin 50mg/ml on alternating hours, and IV Gentamycin 80mg q8h, and Cefazolin 250 mg q6h for five days, and Pred- forte drop qid. He responded well, the hypopyon disappeared after three days and his vision improved. The patient was discharged home on the 6<sup>th</sup> day on oral prednisolone 5mg Bid, fortified Gentamycin and Cefazolin drops qid, and Pred forte qid.

On tapering the medications the inflammation flared up. The patient was admitted to hospital and treated as a case of chronic endophthalmitis secondary to questionable Propriobacterium acne and had vitreous tap for culture and sensitivity. Intravitreal Vancomycin 1mg/0.1ml and Amikacin 0.4mg/0.1ml were given. He was put on Pred forte and Oflox (Ofloxacin) drops Qid. Culture turned to be negative. In spite of the above measures the patient deteriorated. AC tapped and sample was obtained from the white material behind the IOL and Vancomycin and Gentamycin were injected at that area. The patient was put on endophthalmitis treatment regimen. Culture showed coagulase-negative staphylococcus aureus, sensitive to Gentamycin. The patient improved and discharged home on Pred forte gtt Qid and fortified Gentamycin Q3h and oral Prednisolone 20 mg/ day. The treatment was tapered over three weeks and when the Pred forte stopped and the oral Prednisolone dose became 5mg/day the inflammation flared up. Informed consent about using 5-FU injection to control inflammation was taken from the patient before subjecting him to vitrectomy, removal of IOL and intravitreal antibiotic. The patient received three subconjunctival injections of 5-FU 5mg/0.1 ml over three

weeks. The eye became quiet and the white plaque disappeared and his vision improved to 20/25 without medications since then.

#### **Case 4**

A 20 year old male was seen at our uveitis clinic complaining of pain and decrease of vision in the right eye for 3 days. He is a known case of recurrent idiopathic iridocyclitis and was fully investigated 2 years ago at our institute with negative results.

On ocular examination, his best corrected vision was 20/60 OD and 20/20 OS. Pupils were equal and reactive with no RAPD. SL examination of the right eye revealed conjunctival congestion with ciliary flush and deep AC with 3+ cells and flare and posterior synechia at 2 o'clock with normal lens. Fundus examination showed 1+ cells at the anterior vitreous and I.O.P of 16 mmHg in both eyes with normal retina of the right eye. Patient was diagnosed to have right recurrent idiopathic iridocyclitis and was started on Pred- forte drops every hour and Cyclopentolate 1% drops tid. One week later vision improved to 20/40 with 2+ cells and flare. 2 weeks later vision improved to 20/30 with 1+ cell and flare and IOP was 30 mmHg. The patient was started on Cosopt (Dorzolamide/Timolol maleate) drops bid and Pred forte reduced to qid. One week later his IOP dropped to 18 mmHg. Pred forte was reduced slowly over 6 weeks down to once a day and Cyclopentolate stopped. The patient developed recurrence of his uveitis with 4+ cells and flares. Pred forte increased to q 1 h. A week later his inflammation markedly reduced but his IOP increased to 28mmHg. Since the patient was a steroid responder; Pred - forte was replaced by Acular (Ketorolac tromethamine) drops qid. He also was given three injections of 5-FU 5 mg/0.1 ml subconjunctival over three consecutive weeks. His vision improved to 20/20 with complete resolution of iritis and his IOP reduced to 16 mmHg. Acular and Cosopt were stopped after two months with no recurrence of inflammation or glaucoma for more than 12 months of follow up.

#### **Case 5**

A 30 year old male patient with a known history of Ankylosing Spondylitis for 5 years; presented to our uveitis clinic with a history of pain and redness in his right eye for 3 days. He gave a history of recurrent iritis in this eye for the last 18 months. He had 4 attacks, each lasted for 6 to 8 weeks and responded to topical corticosteroids.

On ocular examination, his best corrected vision was 20/50 OD and 20/20 OS. Pupils were reactive OU with no RAPD. SL examination of the right eye revealed ciliary flush with mild diffuse conjunctival congestion, and the anterior chamber was deep with 4+ cells and flare and fine KPs over the lower one third of the endothelium. Iris and lens were normal. Slit lamp evaluation of the left eye was within normal. Fundus exam was normal in both eyes, and the intra-ocular pressure was 16 mmHg OD and 17 mmHg OS.

The patient was diagnosed to have iritis of the right eye and put on Pred - forte drops every hour and Cyclopentolate 1% T/D. Since the attacks were so frequent; he was offered to be treated by 5-FU. Three sub conjunctival injections of 5-FU 5mg/0.1ml each were given over

3 weeks. At the end of the 3<sup>rd</sup> week his visual acuity improved to 20/20, the anterior chamber was clear and IOP was 16 mmHg. Pred -forte was tapered over 6 weeks and he had no recurrence for more than two years.

### **Case 6**

A 36 year-old lady presented to our uveitis clinic with a history of severe pain in her left eye for two weeks. She had left recurrent attacks of iritis for the last 6 years and was fully investigated with no evidence of underlying etiology. She was on Timolol 0.5% eye drops bid to her left eye for the last 3 years. On ocular examination, her best corrected visual acuity was 20/25 OD and 20/100 OS. Pupils were reactive in both eyes with RAPD of OS. SL examination of the right eye was within normal. Left eye showed diffuse conjunctival congestion with mild corneal edema. Anterior chamber was deep with 2+ cells and flares, iris evaluation showed posterior synechiae extending from 12 to 8 o'clock. Lens examination revealed posterior sub-capsular cataract. The vitreous and retina were normal in both eyes. Cup/disc ratio was 0.1 OD and 0.8 OS, with an IOP of 15 mmHg OD and 26 mmHg OS. The patient was diagnosed to have left idiopathic iritis with uncontrolled glaucoma. She was put on Vexol (Rimexolone) 1% drops every hours, Mydriacyl (Tropicamide) 1% tid, and Alphagan (Brimonidine) 0.2% bid. One week later her vision was the same, the anterior chamber evaluation showed 1+ cells and flare and IOP was 23 mmHg. Vexol was reduced to Qid and Acular 0.5% drops Qid was added. Ten days later she was seen, and the anterior chamber showed 1+ cells and flare, with an IOP of 23 mmHg. The Patient was given 3 subconjunctival injections of 5-FU 5mg/0.1ml each over a period of three weeks. At the end of the 3<sup>rd</sup> week, the patient maintained the same visual acuity, the AC showed occasional cells, no flare and IOP was 21 mmHg. Vexol was tapered over 4 weeks and she was kept on Mydriacyl 1% tid, Acular 0.5% QID, Timolol 0.5% bid, and Alphagan 0.2% bid. At 9 months follow up, the anterior chamber was quiet in her left eye and IOP was 18mmHg while she was on above medications.

### **Results**

The demographics and clinical characteristics of the studied cases are shown in Table 1.

**Table 1: The demographics and clinical characteristics of the studied cases**

Case No	Age (years)	Sex	Affected eye	Type of Uveitis	Duration of Uveitis (Years)	Glaucoma	Visual Acuity	IOP (mmHg)	Anterior Chamber Reaction
1	20	Female	Right	Idiopathic	5	Present	20/200	36	2+cells
2	42	Female	Right	Idiopathic	0.5	Present	20/40	50	1+cells
3	78	Male	Left	Secondary to Cortex	0.2	None	20/60	15	4+cells and Hypopyon
4	20	Male	Right	Idiopathic	2	Present	20/60	30	3+cells
5	30	Male	Right	Idiopathic	1.5	None	20/50	16	4+cells
6	30	Female	Left	Idiopathic	6	Present	20/100	26	2+cells

The Effect of Treatment with 5-FU on the Anterior Uveitis cases is presented in Table 2.

**Table 2: The effect of treatment with 5-FU on the anterior uveitis cases**

Case No	Frequency (No of injections)	Visual Acuity	IOP mmHG	Anterior Chamber Reaction	Follow up Period
1	3	20/40	16	None	3 years
2	4	20/20	14	None	2 years
3	3	20/25	14	None	4 years
4	3	20/20	16	None	1 years
5	3	20/20	16	None	2 years
6	3	20/100	18	None	9 months

### Discussion

Five-fluorouracil (5-FU) is a potent antimetabolic agent. It is a pyrimidine base analogue; it has a cell-cycle specific antimetabolic activity that acts during the S phase of the cell cycle. It is converted to 5-F DUMP, which inhibits thymidylate synthetase, preventing DNA and RNA synthesis because of a lack of thymidine. This results in disturbed cell growth and death of cells<sup>[2]</sup>. It controls uveitis by inhibiting the reproductive ability of lymphoid cells, which in turn interferes with its both humoral and cell-mediated immunity<sup>[5]</sup>. It was the first chemotherapeutic agent to be successfully used to reduce filter failure in high-risk surgical cases<sup>[2]</sup>. The first report on the effect of 5-FU in the control of anterior uveitis was published in the literature by Ophir and Ticho<sup>[5]</sup>. They noticed remission of anterior uveitis for about 8 months, in 3 eyes with inflammatory glaucoma, which had filtering surgery. These eyes received one to two subconjunctival injections per day of 5-FU for a duration of 7 to 14 days to prevent bleb scarring.

In our series we described six cases; 5 cases with idiopathic anterior uveitis, and one case (No.3) with chronic secondary anterior uveitis (endophthalmitis). All cases responded well to 5-FU subconjunctival injections, and were free of a relapse for  $\geq 9$  months. We used relatively low total dose (15 -20 mg) of 5-FU comparable to the high dose (35-130 mg) used by Ophir and Ticho.<sup>[5]</sup> This could be the reason that none of our patients had any complication related to 5-FU use. In case (No.2), 5-FU injections were successfully used as an adjunct to MM-C to control inflammation and prevent bleb scarring and failure. In case (No.3), the patient had chronic secondary anterior uveitis (endophthalmitis) after uneventful cataract surgery. He had white posterior capsular plaque from which coagulase-negative Staphylococcus aureus was isolated. Previous studies showed that the plaque consists of a mixture of lens material and colonies of microorganisms<sup>[6-7]</sup>, including coagulase-negative Staphylococcus aureus, which could produce intraocular abscess masquerading chronic uveitis<sup>[8]</sup>. Most cases of chronic infectious postoperative to endophthalmitis will go on to require some type of surgical treatment due to recurrent or persistent inflammation.<sup>[6-7]</sup> This was avoided in our patient by using 5-FU injections.

Glaucoma is most commonly associated with chronic anterior uveitis. It is due to obstruction of the trabecular meshwork by inflammatory cells and debris <sup>[9-10]</sup>, and or Steroid which is used in the treatment of uveitis <sup>[11, 12]</sup>. In conclusion, 5-FU as an anti-inflammatory agent could replace steroid in controlling uveitis and glaucoma secondary to uveitis and or steroid therapy. Long term follow up is needed to confirm its long term efficacy.

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