Outcomes of Biologic treatment for autoimmune uveitis

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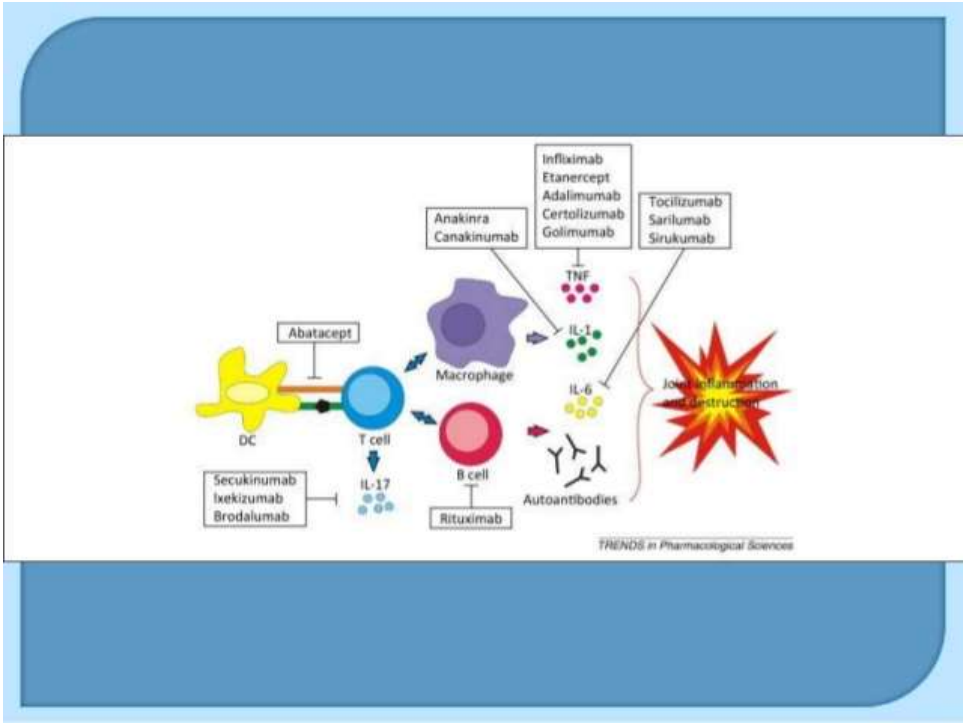
What are biologics?

- Therapeutic proteins designed to block the activity of bioactive mediators of the immune response.
- Most notably recombinant antibodies and antibody-derived proteins

Nomenclature

- Monoclonal antibodies (mAb), when used as medications, are given a generic name ending in "-mab.
- An antecedent "u"(-umab) indicates a human antibody.
- xi"(-ximab) indicates a mixed human-murine (chimeric) antibody.
- Fusion proteins, which typically contain either receptor domains or cell surface markers, are given a generic name ending in "-cept."



- The biologics reviewed here were initially developed to treat systemic inflammatory diseases or to prevent organ transplant rejection, but have been used to treat non infectious uveitis / ocular inflammation, many are being used off-label

- Which Biologic to Use in Uveitis?
- Biologics are relatively new medications, and data on both efficacy and safety of these agents used to treat ocular conditions are limited mostly derived from uncontrolled small case series.

Important classes

- 1- TNF α blockers: infliximab, adalimumab and etanercept
- 2- IL2 blocker: daclizumab
- 3- IL1 blockers: canakinumab
- 4- B cell antagonist rituximab
- 5- lymphocyte co stimulation blocker (abatacept)
- 6- IL-6 blockers e.g. tocilizumab

Lymphocyte inhibitors

- 8- Others: INF
- 9- Anti VEGF drugs
- 10- IVIG

Indications

- Biologics are useful in non-infectious uveitis when:

1-Standard immunosuppression has failed or

2- has been poorly tolerated, or

3- to treat patients with concomitant systemic inflammation that might benefit from these medications

4- As a primary treatment in Behcet's disease

Characteristics, dose and administration

TNF A blockers

Generic name	Trade name	Route	Dose	Adverse effects
Infliximab	Remicade	IV	3-5 mg/kg at week 0 then maintenance at weeks 2,4,6,8 then every 8 weeks	Reactivation of infection (TB, HBV etc), lupus-like syndrome, thromboembolic events, HF, hypersensitivity
Adalimumab	Humira	SC	40 mg every 1-2 weeks. 20 mg/2weeks in children	
Golimumab	Simponi	SC	50 mg monthly	
Cetrolizumab		SC	400 mg at week 0,2,4 then every 4 weeks	

Lymphocyte inhibitors

Daclizumab	Zenapax	IL2 (T cells)	IV, SC	1-2 mg every 2-4 weeks	Hypersensitivity reaction, GI upset, headache
Rituximab	Rituxan	CD 20 (B cells)	IV	500-1000 mg at week 0, 2	PML, infusion reaction, infections
Abatacept		T cells		0.5-1 g at weeks 0,2 then every 4 weeks	Seriuos infections, risk of lymphoma, resp. problems in patients with COPD,

Interferon alpha 2	Cytokine	SC	3-6 mIU/day tapering over 6 months	Injection site reaction, bone marrow suppression
IVIG	Polyclonal AB	IV	0.5 mg/kg for 3 days every month	Transmission of blood borne infections, thrombotic events

Important considerations

T.B	TNF a inhibitors shouldn't be used in patients with history of TB or other infectious uveitis and should be used with caution in patients with positive PPD Coverage with anti-TB is required if potential benefit justifies the risk of TB reactivation
Demyelinating diseases	TNF blockers may cause or worsen demyelinating diseases. Should be avoided in patients with MS and used with extreme caution in patients with intermediate uveitis with neurologic symptoms
Congestive Heart failure	Is worsened by TNF blockers

Malignancy	TNF blockers may be avoided in patients with prior history of malignancy and patients with previous use of alkylating agents because of increased risk of solid tumors.
Vaccination	Live vaccines shouldn't be given concurrently with biologics until three months of discontinuation of biologics. Patients with significant exposure to varicella virus should temporarily discontinue TTT and receive Varicella IG

Second immunosuppressive drug

- A second immunosuppressive agent most typically methotrexate should be given concurrently especially with infliximab to avoid the production of Abs against INFLIXIMAB and subsequent loss of its therapeutic benefit.
- Some authors recommend use with adalimumab also.

Monitoring

- Monitoring by CBC, comprehensive metabolic profile (LFTs and KFTs) at onset of therapy.
- They are repeated at every infusion for infiximab, and every 3-6 months for Adalimmab
- ANA at onset of therapy for TNF blockers (contraindicated in SLE, may cause drug induced lupus).
- IG levels for rituximab

Table 4. FDA Pharmaceutical Pregnancy Categories, Biologic and Immunosuppressive Agents

Pregnancy Category	Description	Examples of Biologics	Examples of Immunosuppressive Agents
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in humans.	None	None
B	Animal reproduction studies have failed to demonstrate a risk to the fetus. There are no adequate and well-controlled studies in pregnant women, or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.	Infliximab, adalimumab, etanercept, certolizumab, golimumab, anakinra, basiliximab	None
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans.	Daclizumab, rituximab, abatacept, efalizumab	Cyclosporine, tacrolimus, mycophenolate mofetil
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans.	N/A	Azathioprine, cyclophosphamide, chlorambucil
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, but the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.	N/A	Methotrexate, leflunomide

Infliximab (Remicade)

- A mixed monoclonal antibody (mAb) composed of human-murine sequences.
- Infliximab has been used successfully in children with non infectious uveitis.
- There are also excellent results reported in adults with Behcet (BD), and other causes of posterior uveitis and scleritis.
- In Japan, recent studies have supported the use of infliximab as first-line therapy for BD.

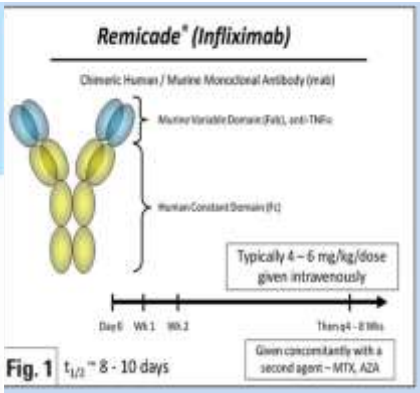
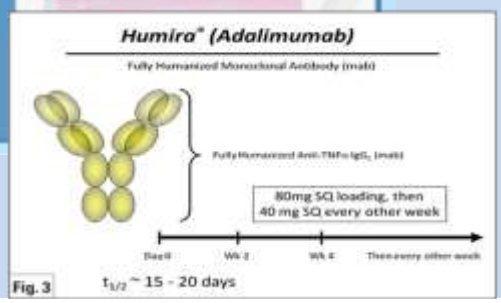


Fig. 1 $t_{1/2}$ ~ 8 - 10 days

- Besides BD and JIA, infliximab has been reported anecdotally to be effective for the treatment of uveitis associated with multiple conditions, including IBD, AS, psoriasis, sarcoidosis, Vogt- Koyanagi-Harada disease, and Takayasu disease.
- It may also be effective to treat birdshot retinochoroidopathy, recalcitrant uveitic cystoid macular edema, pars planitis, multifocal choroiditis, HLA-B27-related anterior uveitis, and idiopathic uveitis.

Adalimumab (Humira)

- Adalimumab (*Humira*) is a fully human monoclonal antibody against TNF-á.
- Due to its promising results and subcutaneous route of administration, experience in both rheumatologic and ocular indications is growing.



- Several reports have demonstrated a successful use of adalimumab in management of BD, severe forms of VKH syndrome, JRA-associated uveitis and idiopathic pediatric uveitis.
- The most common side effect associated with adalimumab is injection-site reaction (10%).
- It is relatively safe and tolerable with rare serious side effects, including serious infections, lymphoma, tuberculosis, herpetic keratitis, opportunistic infections, demyelinating diseases, drug-induced SLE, elevated hepatic enzymes and congestive heart failure.

- HUMIRA is now the first and only FDA-approved non-corticosteroid therapy available for adults with non-infectious intermediate, posterior and panuveitis.
- It found be effective in off-label treatment of pediatric uveitis and scleritis as well.

Description	Cost (€)
Drug prices*	
Adalimumab (Humira 40 mg/0.8 mL ×1 prefilled syringe)	381.39
Etanercept (Enbrel 50 mg/1 mL ×4 prefilled syringes)	756.96
Infliximab (Remicade injectable 100 mg/vial, 1 vial)	426.00
Ustekinumab (Stelara 45 mg/0.5 mL vial, 1 vial)	2,449.81
Resource use	
Subcutaneous injection**	6.64
Day care hospitalization	85.00

Patients and methods

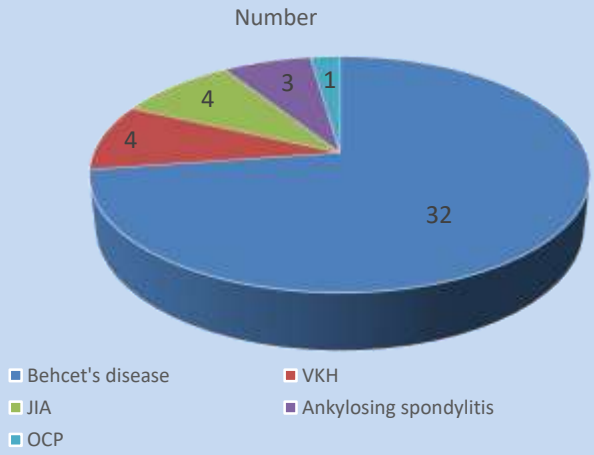
- 44 patients with auto-immune uveitis were treated and followed up with biologic treatment at uveitis service, AUH during the period from Jan 2017 until December 2018
- Patients were previously treated with traditional immunosuppressive drugs with failure of treatment

Treatment failure is defined as one of the following:

- 1. Non-resolution of inflammation, (or failure of complete clinical resolution of the primary lesion in cases of retinitis or choroiditis), at 12 follow-up.
- 2. Recurrence of inflammation described as a two step increase in inflammation as defined by the SUN working group criteria for anterior and intermediate uveitis.

Baseline characteristics

- Out of 198 patients treated from non infectious uveitis in our unit in the period from January 2017 till December 2018, 44 patients met the criteria to receive biologics
- 32 males and 12 females



Protocol

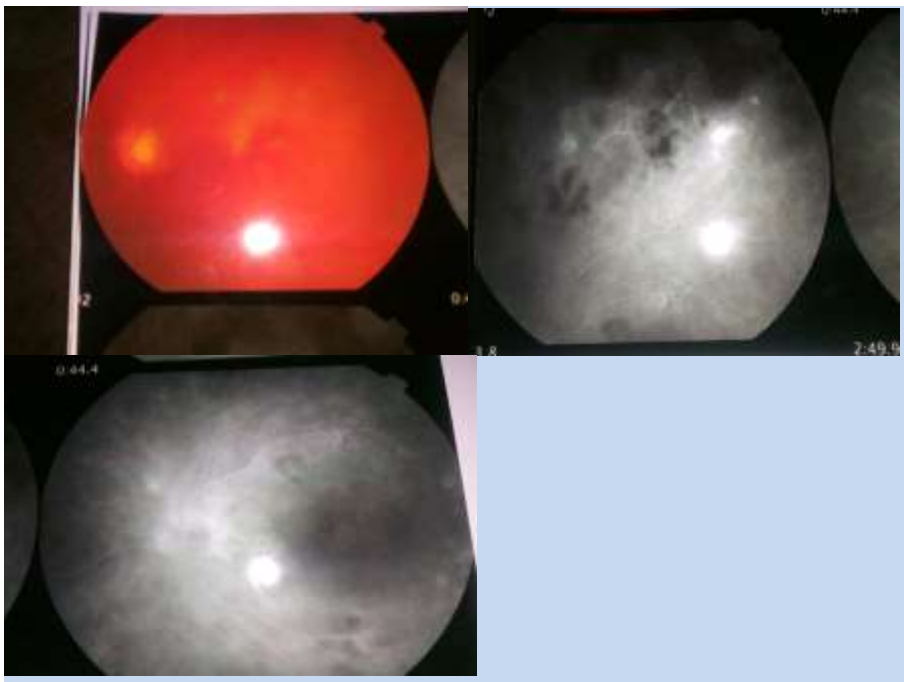
- *Infliximab*
- *Labs: quantiferon Gold, HCV Abs, HBV S Ag, HIV serology , CBC , ANA, Lfts and KFTs*
- *0.5 mg/ kg infusion (at infusion unit) at weeks 0,2,4,6,8 and later every 2 months*
- *Together with 20-25 mg/ week MTX*
- *Steroids according to the cause*

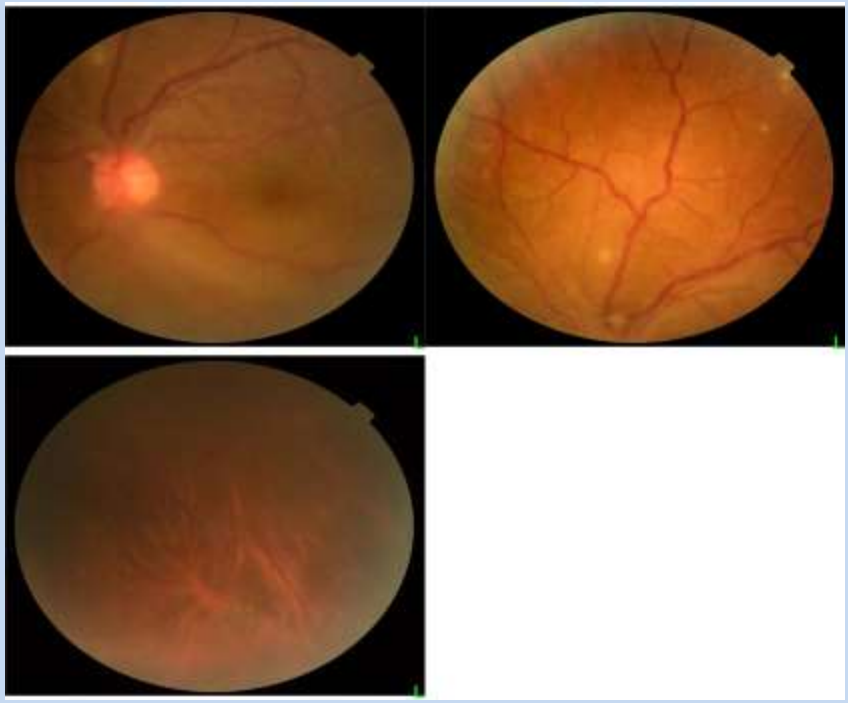
- *Adalimumab*
- *Labs as infliximab*
- *40 mg SC every two weeks in adults and 20 mg in pediatric cases.*
- *May or not add MTX according to doctor's choice*

Results

- Success in 39 patients to decrease inflammation and dependence on steroids.
- Mean oral pred dose 5.79 mg
- 4 patients showed initial good response, later started to wane. 3 of them were on infliximab and one on adalimumab. All failed to adhere to concurrent MTX administration.
- One patient developed pneumonia and passed away.

- Other side effects: reactivation of latent pulmonary TB in one patient despite negative labs before treatment.
- Multiple recurrent chalazia (4 cases)





Conclusions and recommendations

- Biologics are potent new agents approved for a number of rheumatologic conditions. Use in uveitis is largely anecdotal and suggests that some, but not all, patients who are refractory to more traditional immunosuppressive therapies may benefit from biologics

- Increasing evidence suggests particularly promising efficacy in patients with Behcet's disease and JIA
- we recommend working closely with an experienced uveitis specialist and a rheumatologist.

- Due to cost and limited long-term safety data, we continue to reserve biologics for use in patients with uveitis refractory to more traditional immunosuppressive therapies

Thank You