BIOLOŠKA ZDRAVILA ZA ZDRAVLJENJE NE-INFEKCIJSKIH OČESNIH VNETIJ

Zala Lužnik

mentor: doc. dr. Nataša Vidović Valentinčič

MOŽNOSTI ZDRAVLJENJA NE-INFEKCIJSKEGA OČESNEGA VNETJA

nadomeščamo / kombiniramo

STANDARDNO zdravljenje

- PRVO ZDRAVILO: kortikosteroidi (KS)
  - vnetje ne nadzorujemo < 10 mg prednizolona/dan
  - ↓stranskih učinkov zdravljenja s sistemski KS
- → DODATNO IMUNOSUPRESIVNO zdravljenje

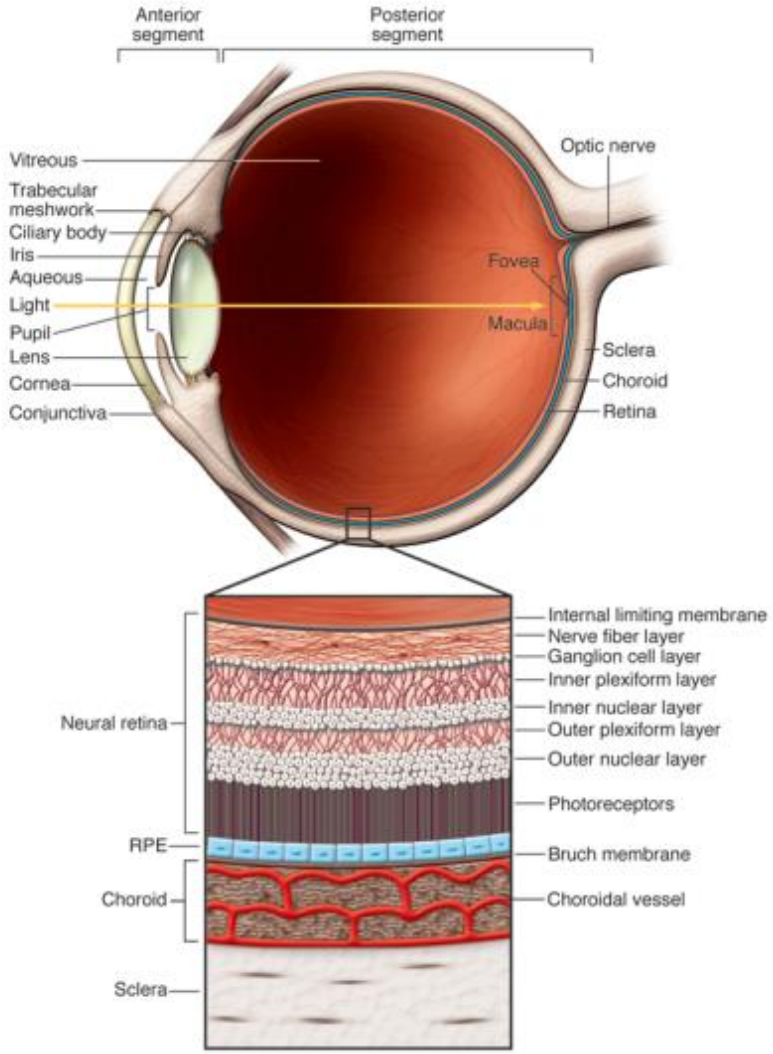
NESTEROIDNA IMUNOSUPRESIVNA ZDRAVILA

- STANDARDNA
  - antimetaboliti (metotreksat, mikofenolat mofetil, azatioprin)
  - T-celični zaviralci (takrolimus, ciklosporin)
  - alkilirajoči agensi (ciklofosfamid, klorambucil)
- BIOLOŠKA ZDRAVILA

Uporaba bioloških zdravil za zdravljenje očesnih vnetij; N Vidović Valentinčič et al; ZV.

NE-INFEKCIJSKE OČESNE BOLEZNI

- KJE vse se uporabljajo BIOLOŠKA zdravila v OFTALMOLOGIJI?
  - UVEITIS
  - skleritis
  - sklerokeratitis
  - idiopatsko orbitalno vnetje...



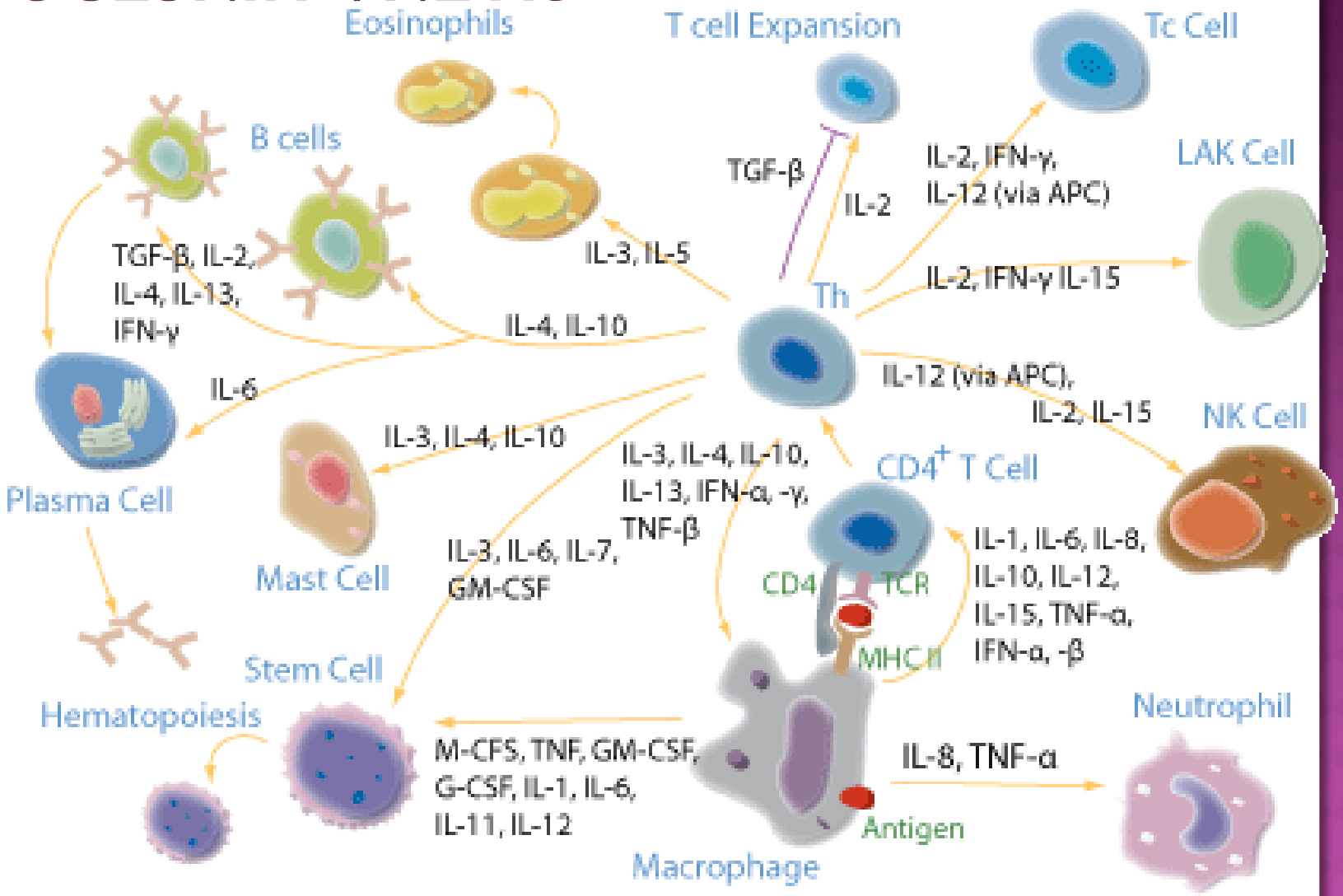
A look at autoimmunity and inflammation in the eye

Rachel R. Caspi

Laboratory of Immunology, National Eye Institute, NIH, Bethesda, Maryland, USA.

Obravnava bolnika z uveitisom; N Vidović Valentinčič; Ješetov dan; Lj 2014

CITOKINI VPLETENI V PATOGENEZO OČESNIH VNETIJ



slike: http://en.wikipedia.org/wiki


INHIBICIJA signalizacije citokinov = ↓ imunsko posredovanega vnetja
← BIOLOŠKA ZDRAVILA

- **BIOLOŠKA ZDRAVILA** – rekombinantni proteini ali monoklonska protitelesa (Ig) → delujejo na specifična tarčna mesta!

UPORABA ¨OFF-LABEL¨

Table 1. Systemic Indications, FDA-Approved Biologics

Biologic Agent	RA	Plaque Psoriasis	PA	CD	UC	AS	JIA	Organ Transplant	NHL	MS
1. Tumor necrosis factor blockers										
Infliximab	+	+	+	+*	+	+				
Adalimumab	+	+	+	+		+	+*			
Etanercept	+	+	+			+	+*			
Certolizumab				+						
Golimumab	+		+			+				
2. Lymphocyte inhibitors										
Daclizumab								+*		
Rituximab	+								+	
Abatacept	+						+*			
Basiliximab								+		
3. Specific receptor antagonists										
Anakinra	+									
Efalizumab		+								
Alefacept		+								
Natalizumab				+						+

RA (Rheumatoid arthritis); PA (Psoriatic arthritis); CD (Crohn's disease); UC (Ulcerative colitis); AS (Ankylosing spondylitis); JIA (Juvenile idiopathic arthritis); NHL (Non-Hodgkin's lymphoma); MS (Multiple sclerosis).
*Also approved for use in children.

Vir: **Use of Biologic Agents in the Treatment of UveitiThese potent new agents may help some patients who are refractory to more traditional immunosuppressive therapies.** Sirichai Pasadhika, MD, Bangkok.2010.

GLEDE NA MESTO DELOVANJA

- MONOKLONSKA PROTITELESA, ki vežejo:
  - citokine:
    - anti-TNFα: infliksimab, adalimumab
    - IL-1 R: anakinra
    - IL-6 R: tocilizumab
  - celične adhezijske molekule:
    - inhibitor kostimulacije T celic (abatacept); protitelesa proti CD 20 (rituksimab)...
  - citokinske R (anti-IL 2 R: daclizumab – 2009 prenehali proizvodnjo)
  - T-celične prepoznavne molekule (anti-CD4)
- topen TNF R: etanercept
- Interferoni

ANTI-TNF IG

Table 2 Characteristics, route of administration, dosage, and potential side effects for selected biologic agents

Generic names	Trade names	Specific target	Route	Dosage	Potential side effects
TNF inhibitors					
Infliximab	Remicade	TNF-α	IV	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	[a]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
Adalimumab	Humira	TNF-α	SQ	40 mg every 1–2 weeks (if bodyweight <30 kg; 20 mg every 2 weeks); loading doses of 80–160 mg are recommended for CD and PsO	
Etanercept	Enbrel	TNF-α,-β	SQ	Adults 50 mg weekly (may be given 50 mg twice weekly for first 3 months for PsO); children 0.8 mg/kg/week (max 50 mg/week)	
Golimumab	Simponi	TNF-α	SQ	50 mg SQ monthly; except for UC 200 mg at week 0, 100 mg at week 2, then 100 mg every 4 weeks	
Certolizumab	Cimzia	TNF-α	SQ	400 mg SQ at weeks 0, 2, and 4, then 200 mg every 2 weeks or 400 mg every 4 weeks	

Vir: Pasadhika et al: Update on the use of systemic biologic agents in the treatment of noninfectious uveitis_2014_Biologics: targets and Therapy

INHIBITORJI LIMFOCITOV

Lymphocyte inhibitors					
Daclizumab	Zenapax	T-cells (IL-2Rα)	IV, SQ	1–2 mg/kg every 2 or 4 weeks	Hypersensitivity reactions, headache, and gastrointestinal disturbance
Rituximab	Rituxan	B-cells (CD20)	IV	500 or 1,000 mg at week 0 and 2; may repeat at 6–12 months thereafter (different regimen for hematologic malignancies)	Susceptibility to infections, infusion reactions, gastrointestinal disturbance, cardiovascular events, muscle spasm, and headache
Abatacept	Orencia	T-cells (CTLA-4)	IV, SQ	Adult RA 500–1,000 mg IV loading, then 125 mg SQ weekly; JIA 10 mg/kg, max 1,000 mg IV at weeks 0, 2, and 4, then every 4 weeks	Susceptibility to infections, allergic reactions, headache, nausea, and malignancy
Basiliximab	Simulect	T-cells (IL-2Rα; CD25)	IV	40 mg IV at weeks 0, 2, 4, 8, and 12	Gastrointestinal disturbance, headache, susceptibility to infections, and hypersensitivity reactions

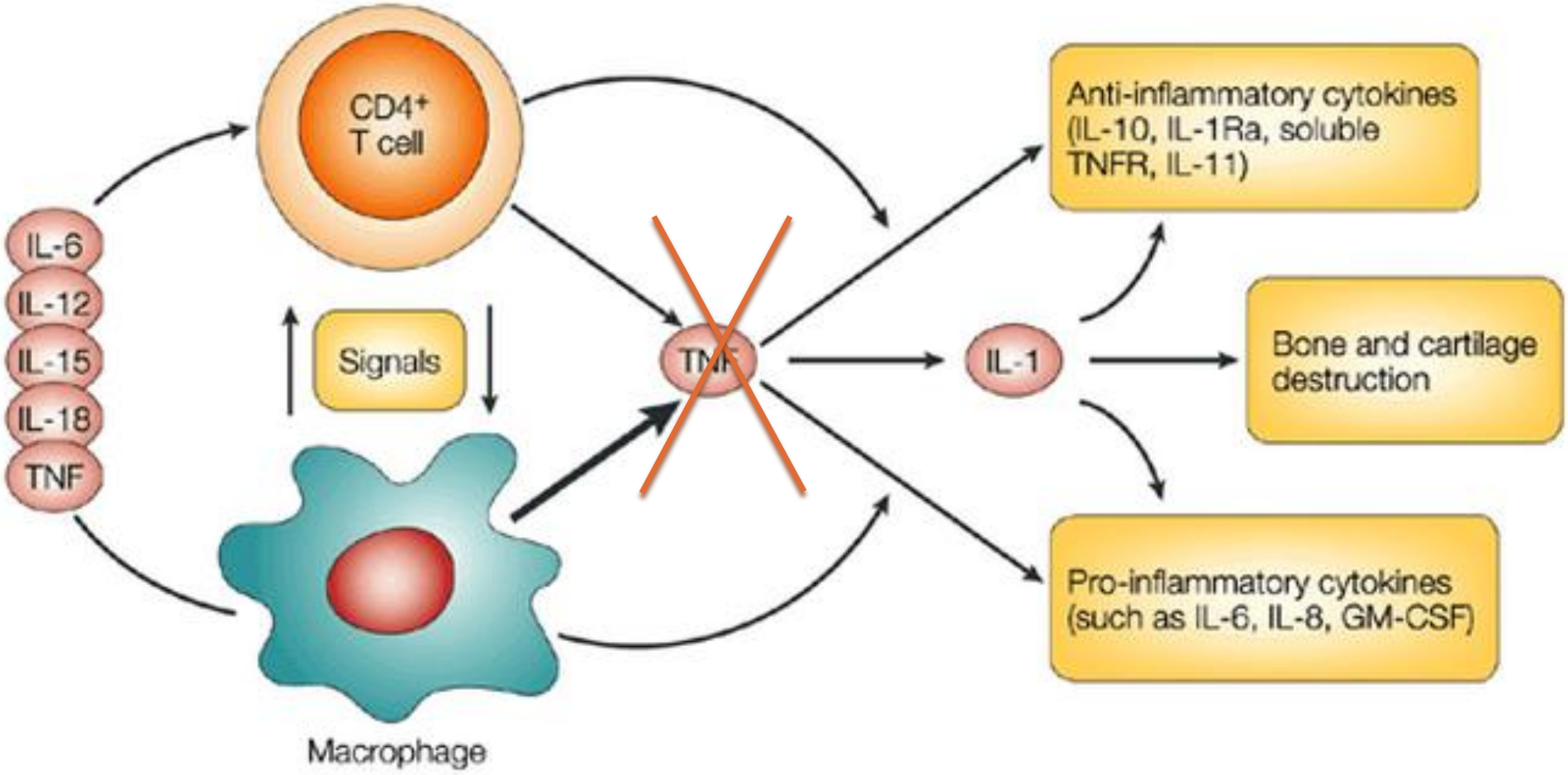
Vir: Pasadhika et al: Update on the use of systemic biologic agents in the treatment of noninfectious uveitis_2014_Biologics: targets and Therapy

SPECIFIČNI ANTAGONISTI R

Generic names	Trade names	Specific target	Route	Dosage	Potential side effects
Specific receptor antagonists					
Anakinra	Kineret	IL-1 receptor	SQ	100 mg SQ daily; children, starting 1–2 mg/kg to max 8 mg/kg daily (dose adjustment for renal insufficiency)	Injection-site reaction, infections, headache, gastrointestinal disturbance, and fever
Canakinumab	Ilaris	IL-1β	IV, SQ	Systemic JIA: 4 mg/kg (max 300 mg) SQ every 4 weeks; CAPS, 2–3 mg/kg SQ every 8 weeks (see text)	Susceptibility to infections, headache, nausea, and abdominal pain
Gevokizumab	(XOMA 052)	IL-1β	IV, SQ	In experiment	Susceptibility to infections and hypersensitivity reactions
Tocilizumab	Actemra	IL-6 receptor	IV	Initial 4 mg/kg IV every 4 weeks, then increase to 8–12 mg/kg every 2–4 weeks	Serious infections, hypersensitivity reactions, and gastrointestinal perforation
Alemtuzumab	Campath	CD52	IV	30 mg IV, 3 days per week for 12 weeks	Cytopenias, infusion reactions, infections, gastrointestinal disturbance, and insomnia
Efalizumab	Raptiva	CD11a	SQ	0.7 mg/kg first dose, then 1 mg/kg weekly (max 200 mg/dose)	Infections, progressive multifocal leukoencephalopathy malignancy, arthritis, and thrombocytopenia
Interferons					
Interferon α-2a	Roferon-A	Nonspecific	SQ	3–6 million units SQ daily, tapering over 6 months	Injection-site reactions, flu-like symptoms, and bone marrow suppression

Vir: Pasadhika et al: Update on the use of systemic biologic agents in the treatment of noninfectious uveitis_2014_Biologics: targets and Therapy

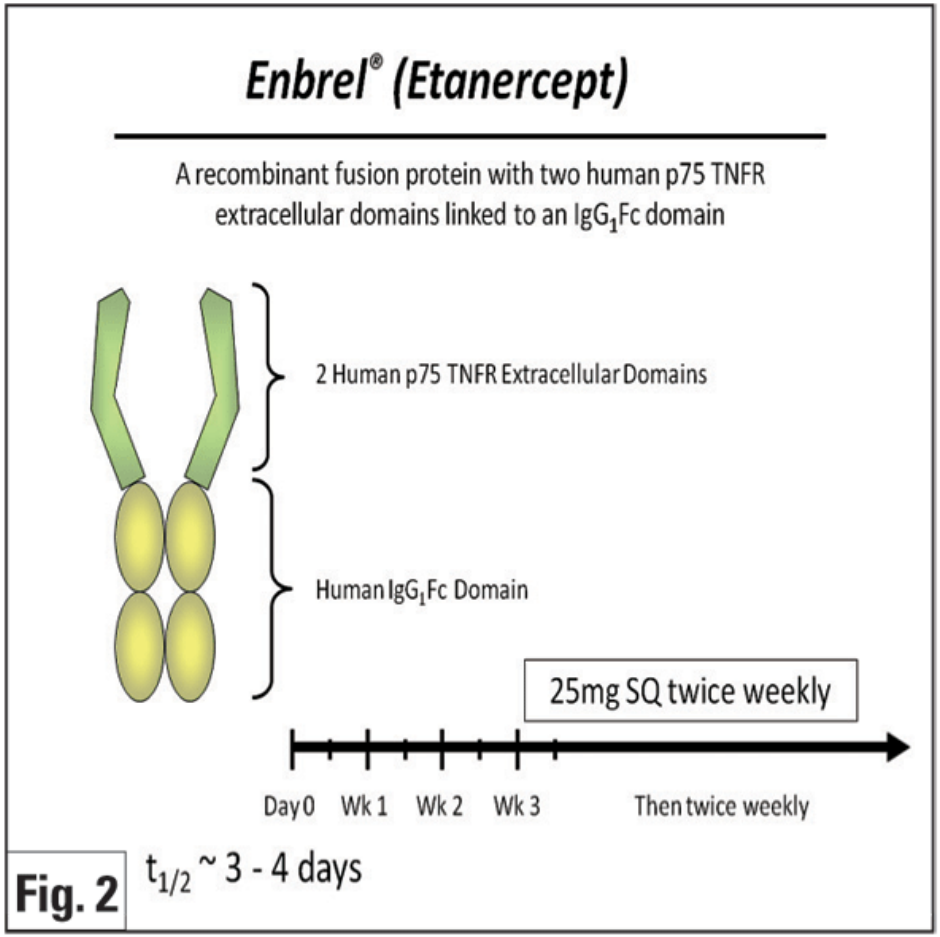
1. PREGLED TNF INHIBITORJEV



Nature Reviews | Immunology

ETANERCEPT (ENBREL)

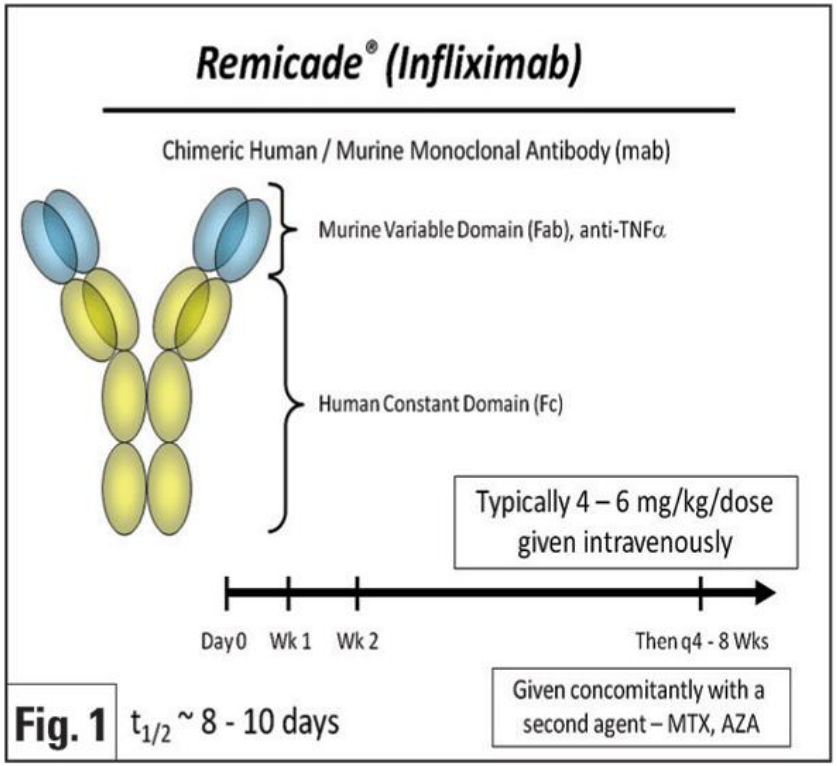
- humaniziran rekombinatni fuzijski protein

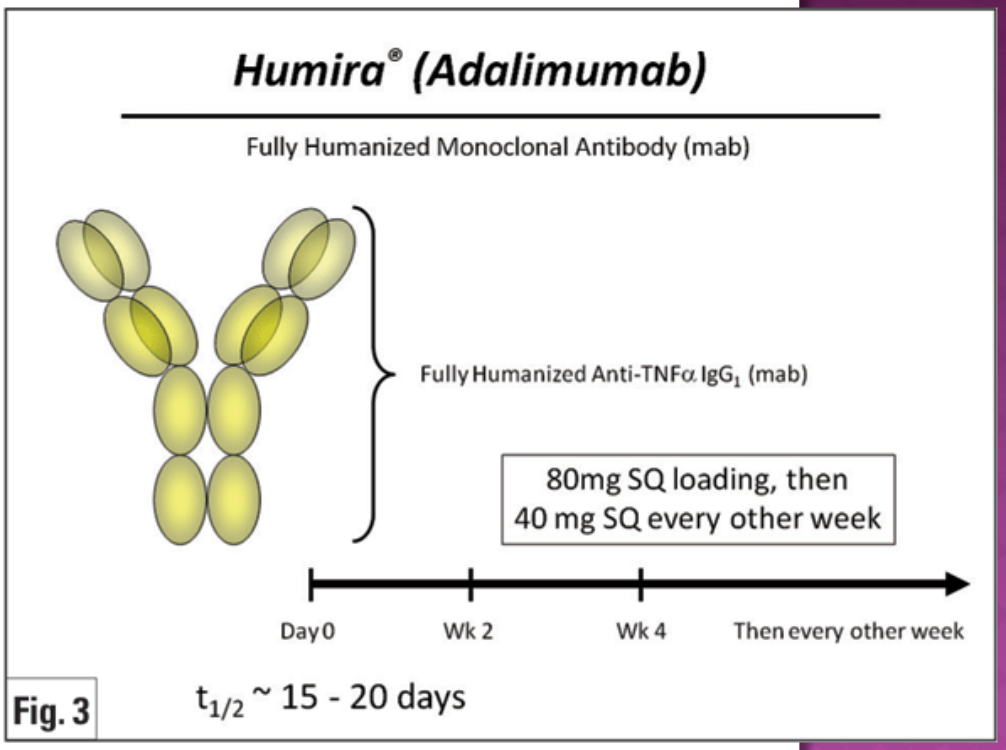


- FDA registriran za: revm. artritis (RA), psoriatični art. (PA), ankilozantni spond. (AS), plakoidno psoriazo (P), poliartikularni JIA
- s.c. 1x/teden ali 2x/teden
- lahko v kombinaciji z metotreksatom, KS, NSAID

Vir: **Use of Biologic Agents in the Treatment of UveitiThese potent new agents may help some patients who are refractory to more traditional immunosuppressive therapies.** Sirichai Pasadhika, MD, Bangkok.2010.

INFLIKSIMAB (REMICADE) / ADALIMUMAB (HUMIRA)





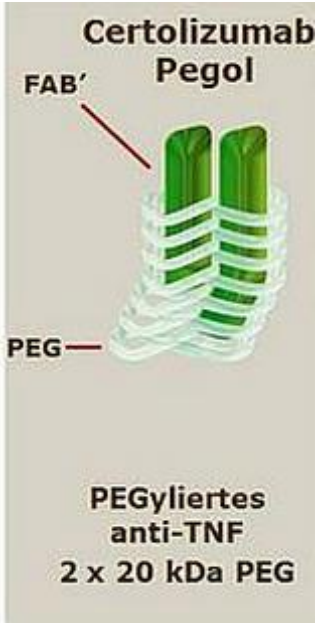
- Infliksimab: FDA: RA,KVČB,AS,PA,P
  - i.v. infuzija in v kombinaciji z MTX
  - zelo učinkovit za (v 1t): Behcet panuveitis, post. uveitis, retinalni vaskulitis (>90%), JIA; + VKH; Takayasu, sarkoidoza...

- Adalimumab: FDA: RA, AS, JIA, PA, KVČB, P
  - s.c.
  - (v 6t): JIA

Vir: **Use of Biologic Agents in the Treatment of UveitiThese potent new agents may help some patients who are refractory to more traditional immunosuppressive therapies.** Sirichai Pasadhika, MD, Bangkok.2010.

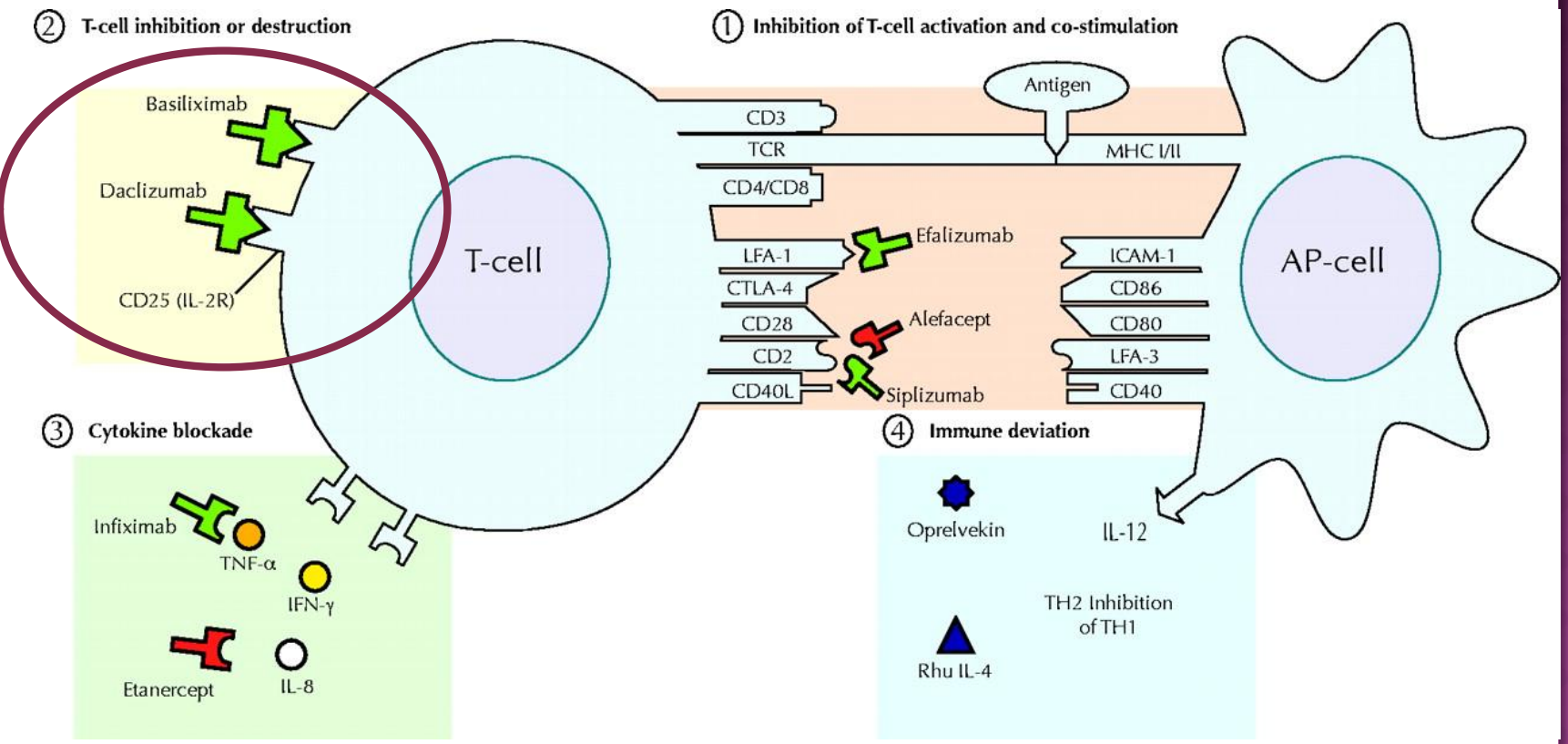
DRUGA LINIJA IZBORA: GOLIMUMAB/CERTOLIZUMAB

- KLINIČNI PRIMERI uporabe pri: JIA-uveitisi (10 pacientov), Behcet sindrom, idiopatskem retinalnem vaskulitisu, AS, HLA-B27+, panuveitis, okluzivni vaskulitis
- **kot druga linija → v primeru neprenašanja infliksimaba, adalimumaba ali slabega odziva na zdravljenje**
  - učinek v 2 tednih
  - certolizumab:
    - 1 klinični primer:
    - uporabe pri pacientu s skleritisom in RA



Vir slika: http://newdrugapprovals.org/tag/certolizumab-pegol/

2. SHEMATSKI PRIKAZ LIMFOCITNIH INHIBITORJEV



Vir slika:
http://www.cmaj.ca/content/170/13/1933/F7.expansion.html

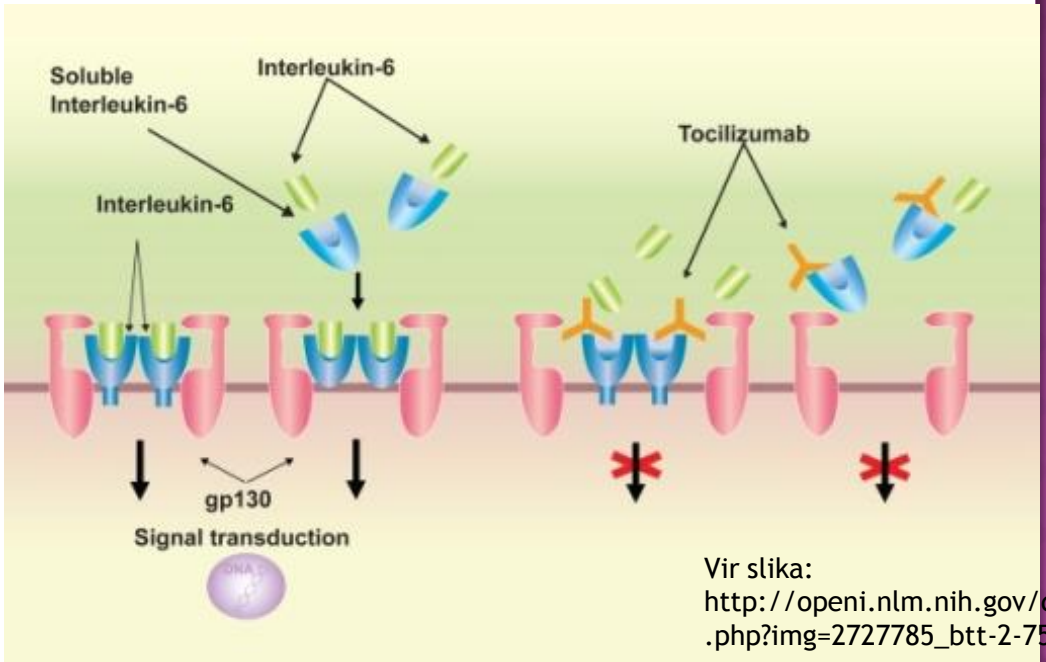
RITUKSIMAB (CD20)

- registriran za: ne-HL, KLL, RA, granulomatozo s poliangiitisom (Wegenerjevo granulomatozo), mikroskopski poliangiitis
- i.v.

- klinični primeri uporabe v oftalmologiji: skleritis, nespecično orbitalno vnetje, JIA-uveitisi, Behcet-uveitis, retinalni vaskulitis.
  - morda za: BSCR, uveitis povezan z esencialno krioglobulinemijo

3. SPECIFIČNI ANTAGONISTI R

- opisani le posamezni klinični primeri uporabe
- kot linija drugega izbora v primeru neučinkovitosti anti-TNF
- Anakinra: le 1 klinični primer opisan (panuveitis v sklopu nevro-kutanega sklepnega sindroma 6 letni deček)
- Canakinumab: Bechcetov sindrom
- Gevokizumab: klinične študije v teku: Bechcetov sindrom - uvitis + retinalni vaskulitis, že v 4 dneh resolucija bolezni
- Tocilizumab



Vir slika:
http://openi.nlm.nih.gov/detailedresult.php?img=2727785_btt-2-75f2&req=4

PREGLED PRIPOROČIL ZDRAVLJENJA OČESNE MANIFESTACIJE VNETJA V SKLOPU SPECIFIČNIH VNETNIH BOLEZNI

KDAJ PRIČETI Z BIOLOŠKIM ZDRAVLJENJEM?

PREISKAVE PRED PRIČETKOM ZDRAVLJENJA?

KATERO BIOLOŠKO ZDRAVILO UVESTI

SPREMLJANJE PACIENTOV NA BIOLOŠKIH ZDRAVILIH

PREGLED NAJPOGOSTEJE UPORABLJENIH BIOLOŠKIH ZDRAVIL

- Metoda: pregled kliničnih študij, preglednih člankov in priporočil
- PRIPOROČILA UPORABE anti-TNF bioloških zdravil (Levy-Clarke et al Marec 2014)
  - ETANERCEPT, INFLIXIMAB, ADALIMUMAB (1)

- pregled bioloških zdravil v oftalmologiji:
  - Pasadhika S in Rosenbaum JT: Update on the use of systemic biologic agents in the treatment of noninfectious uveitis, 2014. Biologics: Targets and therapy.
  - Saadoun et al. Biotherapies in inflammatory ocular disorders: Interferons, immunoglobulins, monoclonal antibodies, 2013. Autoimmunity reviews.

BEHCETOVA BOLEZEN



- očesna prezentacija:
  - uveitis, okluzivni vaskulitis
- Th: sistemski KS + 1< imunomodulatorno zdravilo
- <u>KDAJ uvedba biološkega zdravila?</u>
  - bolezen slabo nadzorovana (> 3 relapsi/leto) s standardno terapijo ali ne prenašanje imunomodulatornih zdravil
  - odgovor 90% (infliksimab)

Several studies have compared patients treated with infliximab retrospectively with those treated with other immunosuppressive therapies. Yamada et al[24,25] retrospectively compared patients treated with either cyclosporine A or infliximab in addition to corticosteroids for ocular Behçet's disease. Both groups had an average of approximately 3 disease exacerbations per year before medication. This was reduced to 1.2 exacerbations in the cyclosporine A group and 0.4 exacerbations in the infliximab group (SIGN level II+). Similarly, Tabbara and Al-Hemidan,[26] in a retrospective study of 43 patients with retinal vasculitis resulting from Behçet's disease, compared relapse rates and visual acuities between patients receiving conventional immunosuppressive medications and infliximab. With a mean follow-up of 36 months, this group found the relapse rate of disease to be significantly higher in the group receiving standard therapy than in the group receiving infliximab. At 24 months, visual acuity was significantly better in the infliximab-treated cohort than in those receiving standard treatment (SIGN level II+).

Markomichelakis et al[27] prospectively compared a single infusion of infliximab with high-dose systemic oral corticosteroids or intravitreal corticosteroids in the treatment of acute exacerbations of ocular Behçet's disease. This group found significantly faster resolution of ocular signs of inflammation in patients receiving infliximab, as well as superior resolution of retinal vasculitis, posterior uveitis, and cystoid macular edema compared with individuals receiving corticosteroid by either route (SIGN level II+).

Okada et al[28] prospectively studied 63 patients with Behçet's disease with ocular manifestations treated with infliximab at 8 tertiary referral centers. At the 1-year time point, 69% of patients showed full improvement in ocular manifestations and 23% showed partial improvement. Only 8% showed no improvement, and no patients showed worsening. The mean number of ocular attacks in a 6-month period decreased from 2.66 at baseline to 0.44 for the first 6 months of therapy. Side effects were noted in 46% of patients, including 3 infusion reactions. However, none of these were considered serious adverse events (SIGN level

Expert Panel Recommendations for the Use of Anti–Tumor Necrosis Factor Biologic Agents in Patients with Ocular Inflammatory Disorders

Grace Levy-Clarke, MD,[1] Douglas A. Jabs, MD, MBA,[2] Russell W. Read, MD, PhD,[3] James T. Rosenbaum, MD,[4,5] Albert Vitale, MD,[6] Russell N. Van Gelder, MD, PhD[7]

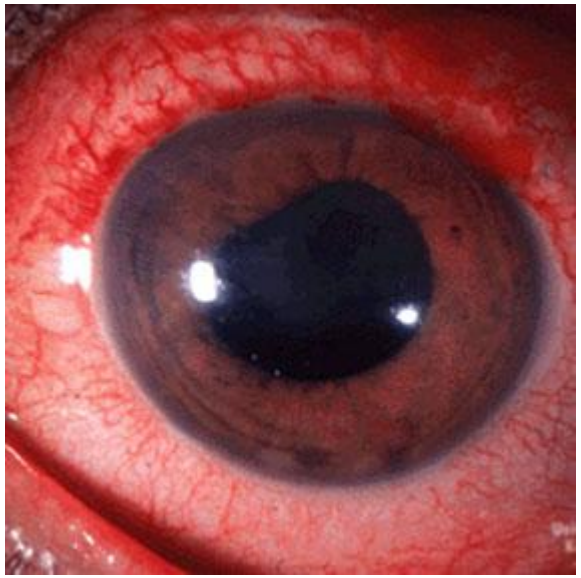
MOČNA PRIPOROČILA ZA OČESNO MANIFESTACIJO:

infliskimab (good-quality evidence) ali adalimumab (moderate-quality evidence)

PRVA ali DRUGA linija ¨steroid sparing¨

infliksimab tudi za akutno poslabšanje pre-eksistentne Behcetove bolezni

SERONEGATIVNI SPONDILOARTRITISI:



- reaktivni artritis
- ankilozantni spondilitis
- KVČB
- psoriatični artritis

- Očesna manifestacija: akutni anteriorni uveitis → redkeje kronično potekajoč
- rekurentno potekajoči (HLA-B27+)

- KDAJ uvedba biološkega zdravila?
  - kronično potekajoč – ‘steroid sparing’
  - KI za klasično zdravljenje / ni odziva

Panel Recommendations for Spondyloarthropathy-Associated or HLA-B27–Associated Uveitis

Strong Recommendation. Infliximab or adalimumab also may be used as corticosteroid-sparing treatment for patients with chronic uveitis resulting from seronegative spondyloarthropathy (good-quality evidence).

Discretionary Recommendation. Infliximab or adalimumab may be used for patients with severe, vision-threatening or debilitating uveitis requiring systemic immunosuppressive agents or as adjunctive therapy to corticosteroid treatment in acute disease (good-quality evidence).

SARKOIDOZA

- 26% pacientov očesno prizadetost
  - adalimumab: 85% uspešnost pri zdravljenju post. očesne prizadetosti neodzivne na KS in metotreksat
- NE etanercept! → poslabšanje granulomskega uveitisa

Panel Recommendation for Treatment of Ocular Involvement of Sarcoidosis with Infliximab or Adalimumab

Discretionary Recommendation. Infliximab or adalimumab may be considered as second-line immunomodulatory therapy for patients failing or intolerant of standard immunomodulatory agents (moderate-quality evidence).

Discretionary Recommendation. Etanercept should not be used in the treatment of ocular sarcoidosis (moderate-quality evidence).

JUVENILNI IDIOPATSKI ARTRITIS - IRIDOCIKLITIS

- infliksimab / adalimumab: second-line imunomodulatorna terapija
- vid-ogrožajoče vnetje v sklopu JIA z nezadostnim učinkom metotreksata ali neprenašanja
- etanercept NE → sekundarni uveitis

POSTERIORNI UVEITIČNI SINDROMI / PANUVEITISI:

- študije na majhni skupini pacientov, klinični primeri
  - Birdshot horioretinitis: infliksimab: 89% uspešnost pri refraktornih pacientih na standardno zdravljenje
  - VKH, multifokalni horoiditis, idiopatski pars planitis (pred uvedbo MR glave za izključitev demilinizacijskih lezij), serpingiozni horoiditis
  - pri idiopatskih oblikah poročano več stranskih učinkov

- Kdaj? second line – steroid sparing pri kronično potekajočih oblikah ali vid ogrožajočih vnetjih

DRUGA OČESNA VNETNA STANJA

- SKLERITIS: kronični / hudo vnetje
- Infliksimab – second-line steroid sparing therapy
- v sklopu granulomatoze s poliangiitisom (Wegenerjeva granulomatoza): rituksimab

POVZETEK INDIKACIJ: KDAJ UVESTI BIOLOŠKA ZDRAVILA?

- bolezen slabo nadzorovana / ni odzivna na standardno imunosupresivno / imunomodulatorno terapijo
- pacienti ne prenašajo standardne terapije (imunomodulatorna zdravila)
- izjemno huda vid ogrožajoča vnetja (BEHCET ZGODAJ ODLOČATI ZA ZDRAVLJENJE)
- otroci: takojšnje agresivno zdravljenje za preprečitev kasnih posledic, ohranitev vida, SU
- infliksimab + metotreksat (manjši stranski učinki)

PREISKAVE PRED APLIKACIJO

- KKS, CRP, SR, jetrni testi, urea, kreatinin, elektroliti
- presejalni testi za tbc!
  - → LATENTNA TBC: zdravljenje (z anti-TNF zdravljenjem lahko pričnemo po 1 mesecu th)
- intermediarni uveitis → MR glave
- cepljenja: pnevmokok, INF, HBV
  - NE-cepiv: živ virus (rabies, polio, VZV)

- APLIKACIJA: sistemsko DA
  - / intravitrealno (infliksimab) študije na živalih?
  - rituksimab

KONTRAINDIKACIJE ZA ZDRAVLJENJE

- aktivna okužba
- < 5 let zdravljena limfoproliferativna bolezen
- zmerno/hudo srčno popuščanje
- kronični HCV/HBV
- demielinizacijska bolezen
- pnevmonitis (Caplanov sy)
- **1 teden pred in 1 teden po operacijah (NE OČESNE – low risk)**
- nosečnost – FDA kategorija B

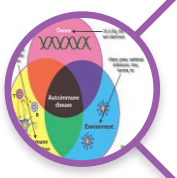
STRANSKI UČINKI ZDRAVLJENJA Z BIOLOŠKIMI ZDRAVILI



ALERGIČNE REAKCIJE

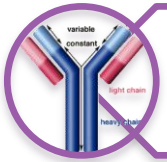


OKUŽBE (REAKTIVACIJA TBC, inv. GLIVIČNA OBOLENJA) - redko

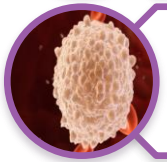


paradoksalna AVTOIMUNA OBOLENJA

(poslabšanje ali de novo demielinizacijska obolenja, (ANA +, dsDNA +) → drug-induced LUPUS)



IMUNSKO-POSREDOVANA REZISTENCA



MALIGNOMI – limfomi??

new-onset UVEITIS (etanercept > infliksimab ali adalimumab) Lim et al.

NAČINI DOZIRANJA

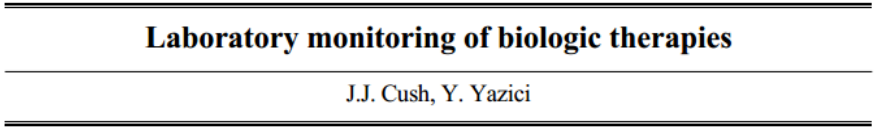
Table 2. Characteristics, Dosage, Administration and Side Effects

Generic Name	Trade Name	Type	Specific Target	Route	Dosages	Potential Adverse Effects
1. Tumor necrosis factor blockers						
Infliximab	Remicade	Chimeric (murine/ human)	TNF-α	IV	3 to 5 mg/kg loading at week 0, two, six, then maintenance 3 to 10 mg/kg every four to eight weeks; max. dose 20 mg/kg in children	Susceptibility to infections, including reactivation of tuberculosis, histoplasmosis and hepatitis B; demyelinating disease; lupus-like syndrome; malignancy; thromboembolic events; hypersensitivity reactions; heart failure
Adalimumab	Humira	Humanized	TNF-α	SQ	40 mg every one to two weeks (if BW<30 kg; 20 mg every two weeks); loading doses of 80 to 160 mg recommended for Crohn's disease and plaque psoriasis	
Etanercept	Enbrel	Protein fusion with human Ig	TNF-α,-β	SQ	Adults 25 mg twice a week or 50 mg once a week; children 0.8 mg/kg/week (max 50 mg/week)	
Certolizumab	Cimzia	Humanized	TNF-α	SQ	400 mg at week 0, two, four then every four weeks	
Golimumab	Simponi	Humanized	TNF-α	SQ	50 mg monthly	
2. Lymphocyte inhibitors						
Daclizumab	Zenapax	Humanized	T cells (IL-2)	IV, SQ	1-2 mg/kg every two or four weeks (see text)	Hypersensitivity reactions; gastrointestinal upset; headache
Rituximab	Rituxan	Chimeric (murine/ human)	B cells (CD20)	IV	500 or 1,000 mg at week 0 and two	Infusion reactions; severe mucocutaneous reactions; progressive multifocal leukoencephalopathy; hypertension; nausea
Abatacept	Orencia	Protein fusion with human Ig	T cells (CTLA-4)	IV	500 or 1000 mg at week 0, two, four then every four weeks (children 10 mg/kg, max 1,000 mg)	Serious infections; allergic reactions; malignancy; respiratory problems in patients with chronic obstructive pulmonary disease
Basiliximab	Simulect	Chimeric (murine/ human)	T cells (IL-2Rα; CD25)	IV	40 mg at week 0, two, four, eight and 12	Gastrointestinal side effects; headache, urinary tract infection
3. Specific receptor antagonists						
Anakinra	Kineret	Humanized	IL-1 receptor	SQ	100 mg daily	Injection-site reaction; infections, especially if concurrently used with TNF-inhibitors
Efalizumab	Raptiva	Humanized	CD11a-receptor	SQ	0.7 mg/kg first dose, then 1 mg/kg weekly (max 200 mg/dose)	Infections; progressive multifocal leukoencephalopathy; malignancy; arthritis; thrombocytopenia
Alefacept	Amevive	Protein fusion with human Ig	CD2-receptor	IM, IV	15 mg IM weekly or 7.5 mg IV weekly for 12 weeks	Hypersensitivity reactions; infections; malignancy
4. Other						
Interferon α-2a	-	Cytokine	Non-specific	SQ	3 to 6 million IU/day, tapering over six months	Injection-site reactions; flu-like symptoms; bone marrow suppression
Intravenous immunoglobulin	-	Polyclonal antibody	Non-specific	IV	0.4 gm/kg for five days/month, or 0.5 gm/kg for three days/ month	Transmission of blood-borne infectious agents; thrombotic events

Vir: **Use of Biologic Agents in the Treatment of UveitiThese potent new agents may help some patients who are refractory to more traditional immunosuppressive therapies.** Sirichai Pasadhika, MD, Bangkok.2010.

SPREMLJANJE BOLNIKOV NA BIOLOŠKIH ZDRAVILIH

- osnovni laboratorij: KKS, jetrna in ledvična funkcija, vnetni parametri
- **1x/3mes prvih 12 mes**
  - v začetku zdravljenja: infliksimab → pred iv infuzijo
  - adalimumab: 1x mesečno v začetku uvajanja zdravljenja, nato 1x/6mes
- ANA, ENA: če se pojavijo znaki lupusu podobnega sindroma
- pozorni na zaplete: srčno popuščanje, reaktivacija tbc, okužbe...



PRIKAZ KLINIČNEGA PRIMERA



8-LETNI DEČEK ŽIGA

2013
NOVEMBER

2014 OKTOBER

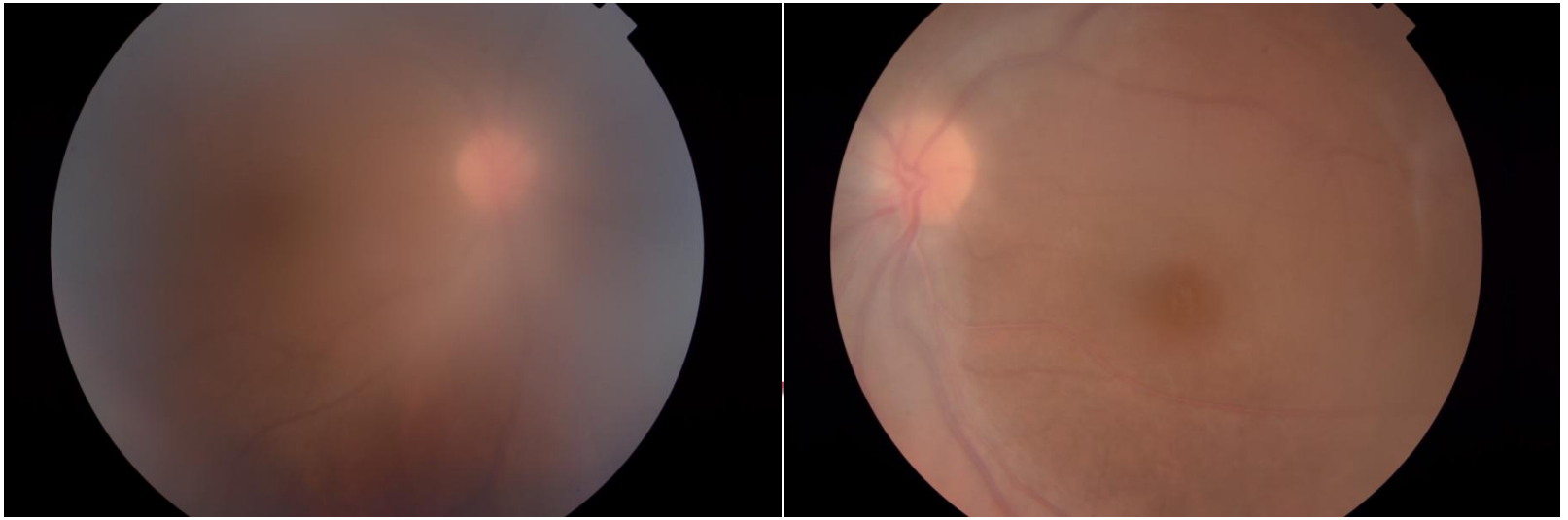
21. 11. 2013 – prvič pregledan ambulantno

zaradi: nekaj tednov težave (izrazita fotofobija), opazili poslabšanje vida

Pridružene bolezni: ZDRAV

Družinska anamneza pozitivna za demielinizacijska obolenja.

Dg: intermediarni uveitis → napoten za sprejem za nadaljno diagnostično obravnavo



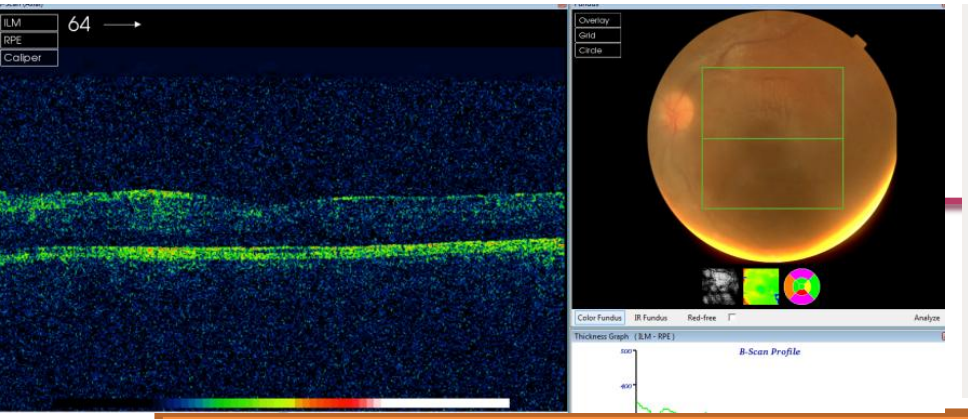
2.12.2013 – HOSPITALIZACIJA

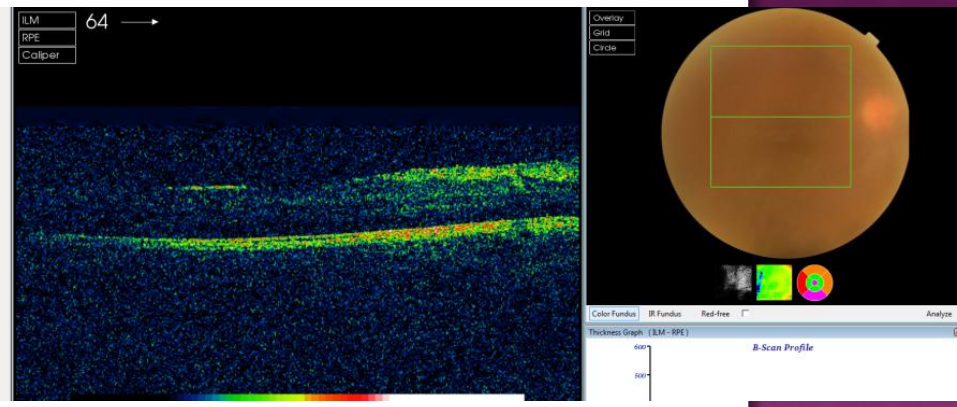
Vdo: 0,2 sc, stenopeično ni bolje, kor. ne sprejme
Vlo: 0,4 sc= stenop., kor. ne sprejme

BM DLo: zrkli bledi, roženici gladki, čisti, Tyndall neg., prekata ustrezno globoka, leči čisti, zenici prostih robov, se ustrezno širita po midriatikih, obojestransko vsaj delno odstopli steklovini, porušene zgradbe, goste motnjave v steklovini, celice relativno redke, nekaj belih motnjav v smislu snežnih kep tako levo kot desno.

Fundus: DLo: papili vidnih živcev rožnati, jasnih mej, v nivoju, kolikor pregledno je klinično žilje v mejah normale, prav tako zadajšnji pol, kolikor pregledno brez žarišč in brez evidentnih znakov periferne patologije, mrežnica leži.

8-LETNI DEČEK ŽIGA





2.12.2013 – HOSPITALIZACIJA

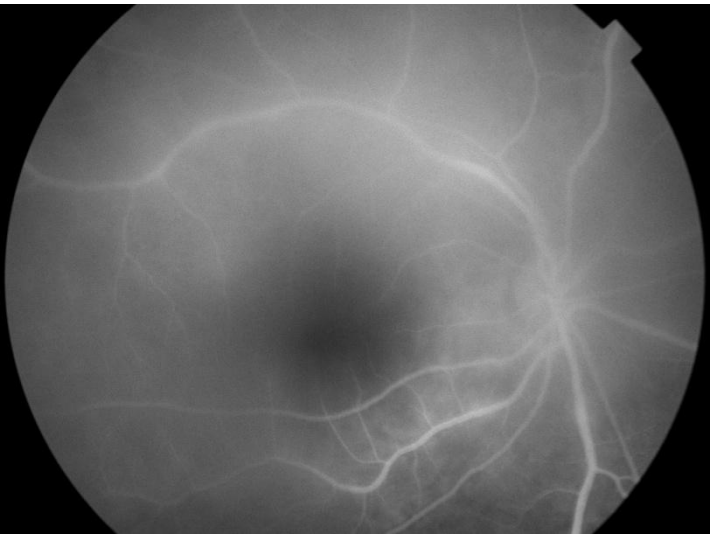
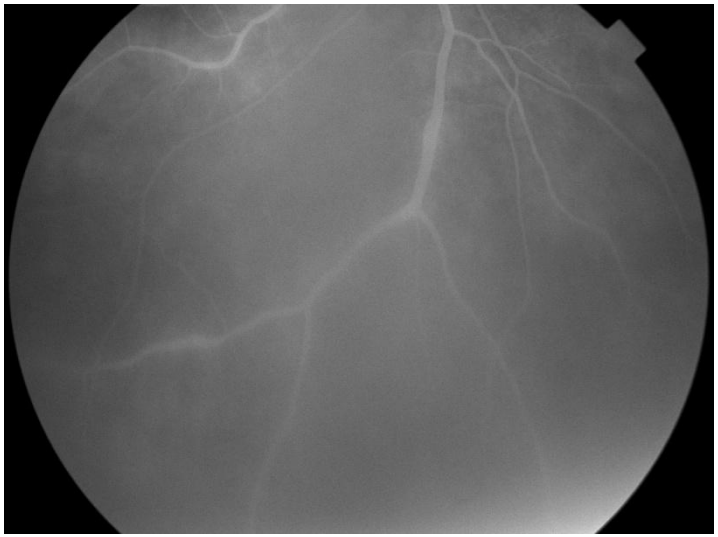
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Vlo: 0,4 sc= stenop., kor. ne sprejme

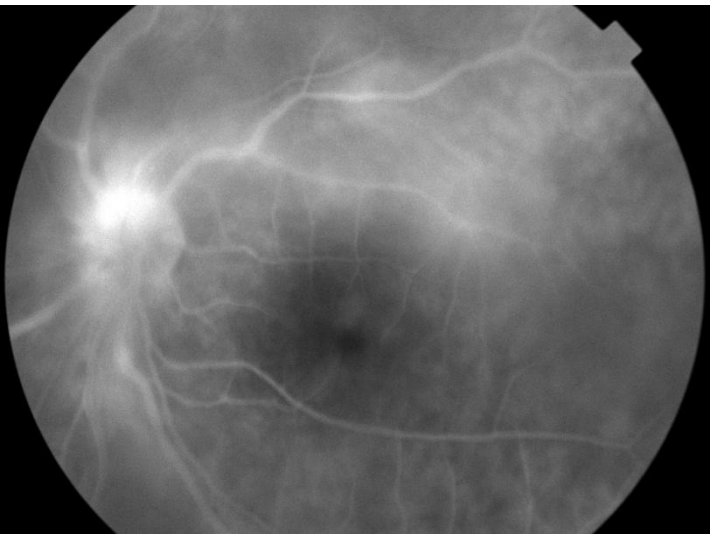
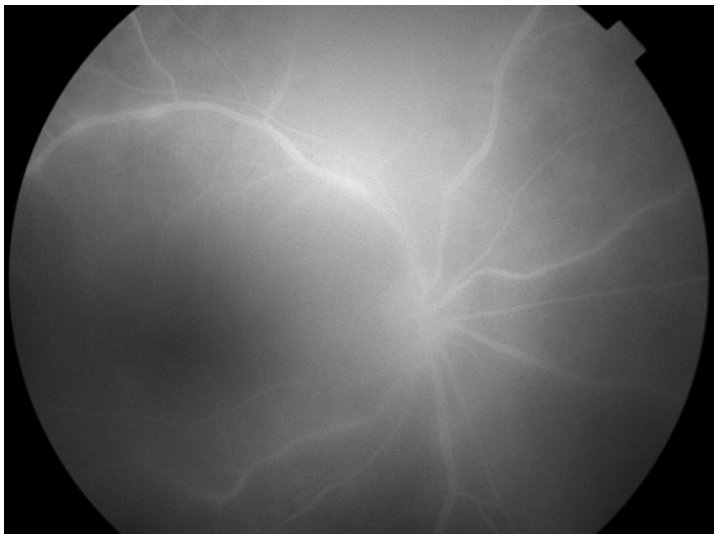
OCT: debelina mrežnic dobrih 300 mikronov, brez evidnetnega CME

UZ: : Do: V odstopli steklovini so rahle nehomogene motnjave. V vitrealnem prostoru so rahle difuzne motnjave. Mrežnica UZ povsod leži. Horioretina UZ ne kaže patoloških sprememb. Papila otičnega živca je v nivoju mrežnice.

Lo: Goste nehomogene motnjave v steklovini z vmestnimi likvificiranimi področji. Temporalno periferno so vidne horioretinalne srednje reflektivne membrane. Mrežnica UZ leži. Horioretina UZ brez patoloških sprememb. Papila vidnega živca je v nivoju mrežnice (Vladimir Debelič, dr.med.).

FA Topcon: dec 2013
DESNO: Širše vene, segmentno barvanje žilnih sten ven, hiperemična papila. Ni edema v makuli.
FA slike slabše zaradi motnjav v steklovini.
LEVO: Podobna slika kot desno.


8-LETNI DEČEK ŽIGA

DECEMBRA:
uveden MEDROL,
METOTREKSAT

2013
NOVEMBER

2014 OKTOBER

2.12.2013 – HOSPITALIZACIJA MNENJE:

Po razgovoru z revmatologinjo dr.Toplakovo ob zadnjem pregledu klinično ni povezave očesne bolezni s prepoznano sistemsko boleznijo ali infekcijskim vzrokom – vse izključeno.

TERAPIJA: Po dogovoru z revmatologinjo uvedba sistemskega zdravljenja s kortikosteroidi in Methotrexatom.

9.12.2013: uveden Medrol 2x10mg

8-LETNI DEČEK ŽIGA

JANUAR: kontrola:
M↓, MTX

2013
NOVEMBER

2014 OKTOBER

2.1.2014
V do:0,8p sc; lo: 0,7p sc (kor. ne sprejme)
BM: v steklovini še obilna eksudacija, ki pa je nekoliko zmanjšana

OCT: ni edema v makuli.

Th: Medrol 12mg po, revmatolog predpis vzdrževalne doze 4 mg še do februarja. Vzporedno v dec. pričel prejemati Metotreksat.

SLEDENJE - AMBULANTNE KONTROLE

MAREC 2014	APRIL 2014	JULIJ 2014
na sistematskem pregledu slabši vid, subjektivno ?; nosi očala V do: 0,7p sc; 0,8p cc; lo: 0,6p sc; 0,7p cc Status: v steklovini celice ++, Papili intenzivneje rožnati Th: Medrol 2 mg/ vsak drugi dan še za 1 mesec, MTX 15 mg	subjektivno slabše V dlo: 0,6p sc Status: ozadje: hiperemični papili, v makuli nekaj patoloških refelksov, periferno ob žilah obloge FA: vene so bolj izrazito obarvane, več puščanja, brez edema v makuli Th: MTX 15mg, Folacin Uvedba Metojecta z dr. Toplakovo	subjektivno in klinično ni odgovora na sc MTX slabše V do: 0,4p - 0,7p sc; lo:0,4p-0,5p sc FA: vene so širše, na številnih mestih se segmentno barvajo, v poznih fazah se barva tudi papila. Arterije bp. Makula brez edema. Th: UVEDBA BIOLOŠKEGA ZDRAVLJENJA z ADALIMUMABOM

8-LETNI DEČEK ŽIGA

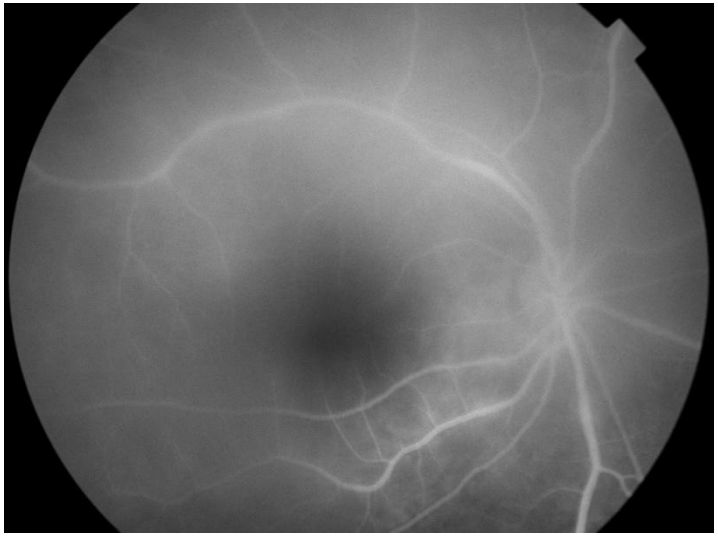


2013
NOVEMBER

2014 OKTOBER

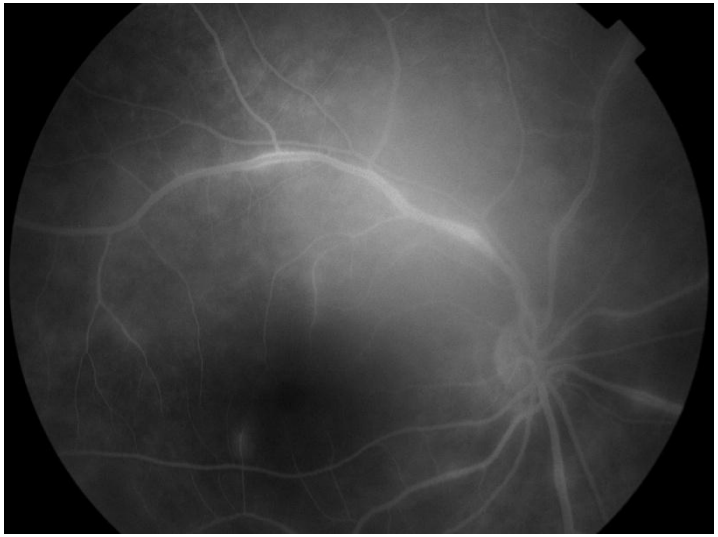
V do: 0,6p; lo: 0,7p sc
Terapija: Humira / 2 tedna; MTX 1x/teden

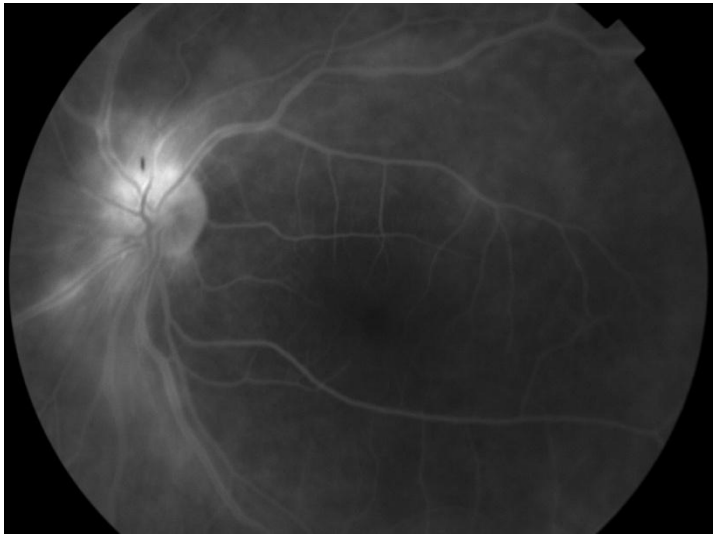
Dec 2013: Pred uvedbo terapije



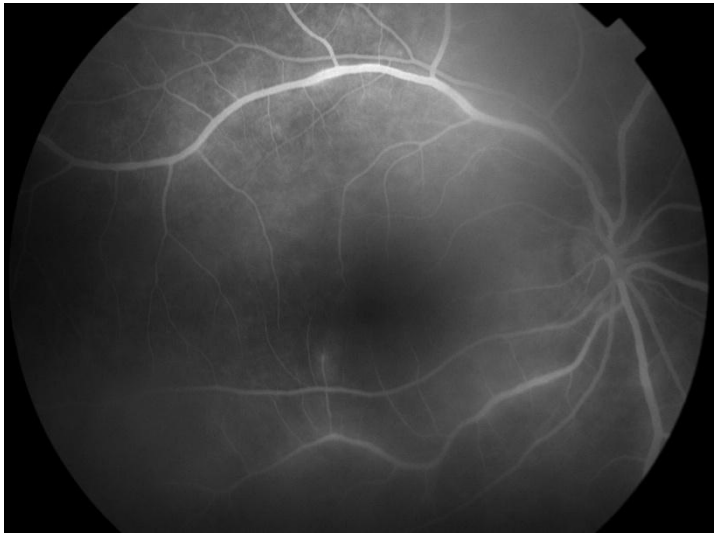


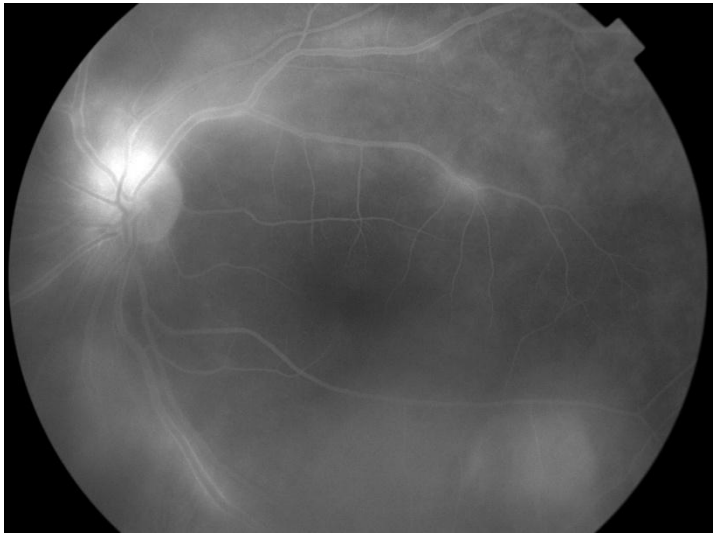
April 2014: po th z Medrolom in na MTX





2014 junij: Pred uvedbo adalimu.



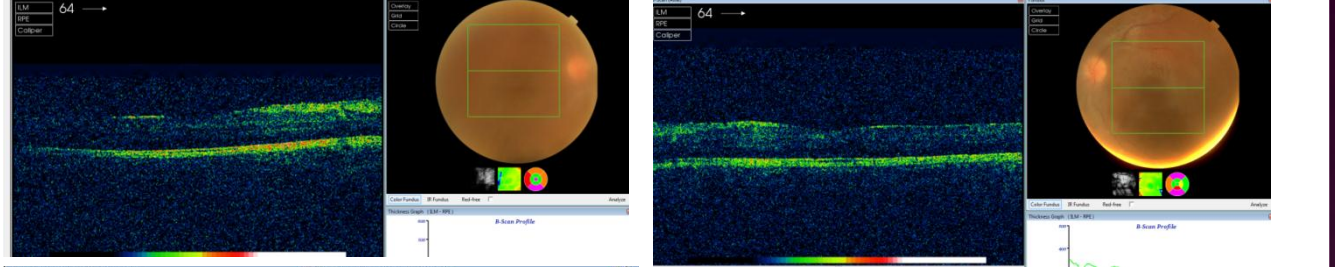


Oktober: po th z adalimu mabom +MTX

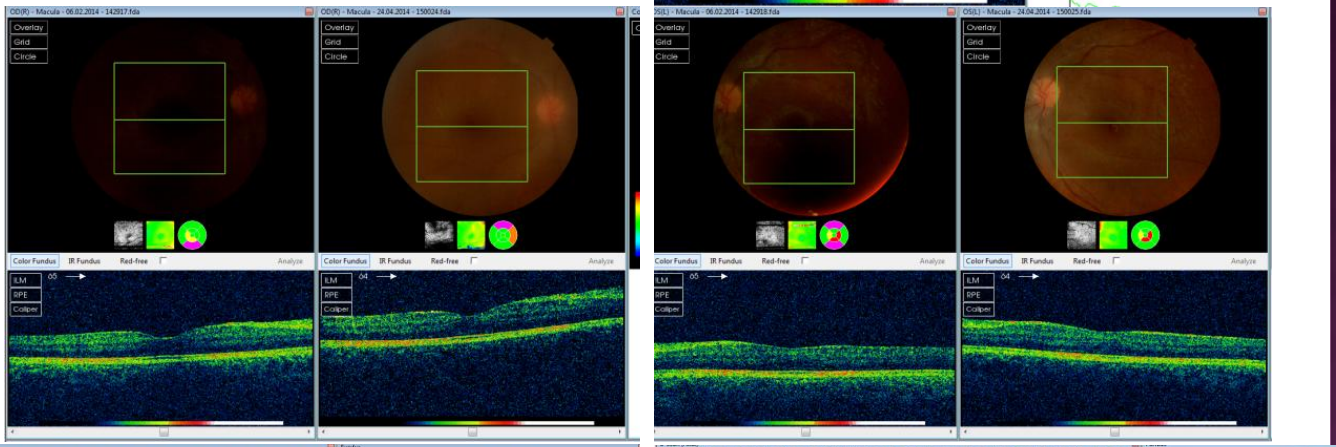




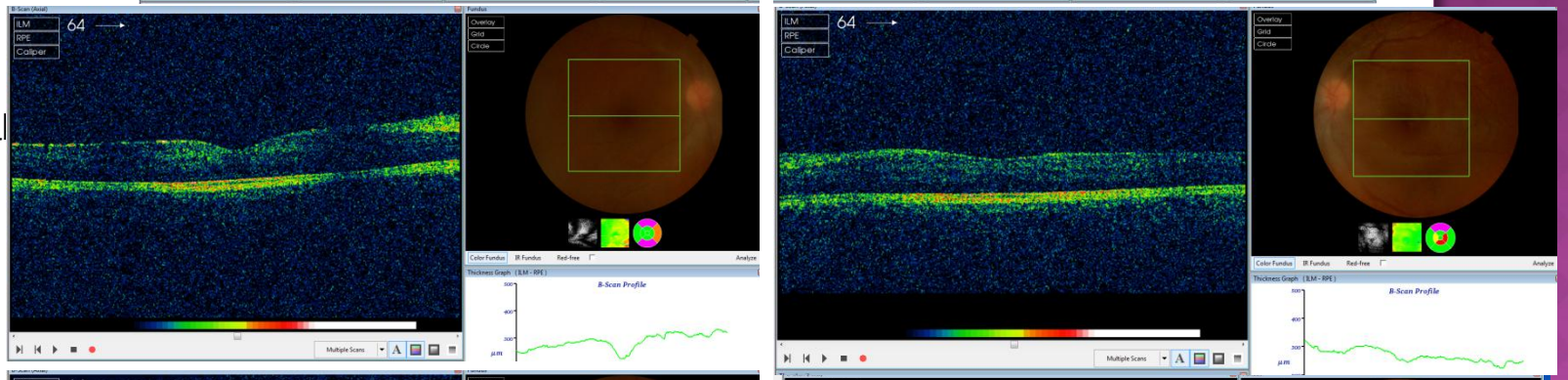
Pred uvedbo terapije – 2013 dec:



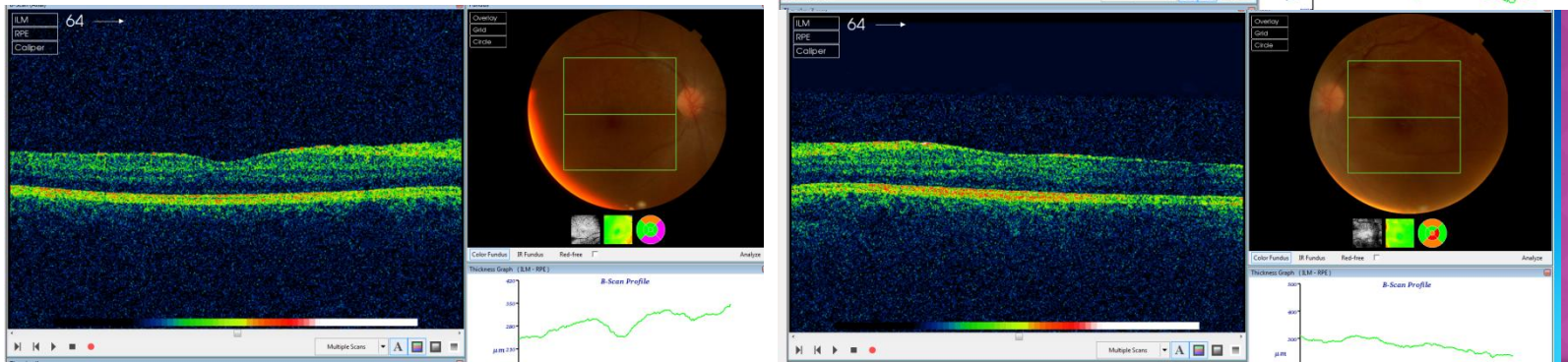
Feb-April 2014: po th z Medrolom in na MTX



Pred uvedbo adalimumab a – 2014 junij:



Oktober 2014: po th z adalimumabom +MTX





HVALA ZA POZORNOST ☺