Varnost klasičnih imunomodulatornih zdravil

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Imunomodulatorna zdravila (IMT)

- IMT oslabijo delovanje imunskega sistema
- zmanjšajo vnetni odziv
- uporabljajo se pri transplantacijah organov, avtoimunih obolenjih in rakavih obolenjih
  - neinfekcijski uveitisi
  - skleritisi
  - sarkoidoza
  - multipla skleroza
  - Crohnova bolezen
  - revmatološka obolenja (RA, SLE, vaskulitisi)

Alex F. Et al. 2014
McDonald JW et al. 2012
Cleqq A et al. 2001
Robert PB et al. 1999

Zakaj je pomembno poznavanje IMT?

- večina oftalmologov uporablja previsoke vzdrževalne odmerke kortikosteroidov
- samo 12% pacientov z uveitisom prejme IMT
- 75% oftalmologov ne pozna smernic zdravljenja
- monoterapija s kortikosteroidi praviloma ne privede do stabilne remisije
- kortikosteroidi imajo več stranskih učinkov
- IMT ima manj komplikacij
- IMT ima večji potencial za dolgotrajno remisijo

Nguyen et al. 2011
Jeas S. 2011
Marianne D. 2012

Uveitis je heterogena skupina bolezni

- približno 30 vzrokov
- prvi korak pri zdravljenju je natančna opredelitev bolezni
- osnovno zdravilo so kortikosteroidi
- IMT uvajamo če:
  - je prisotna vzročna sistemska bolezen
  - je prisotna določena uveitična entiteta (Behcet, Simpatična oftalmija, VKH, revmatoidni skleritis)
  - pacient ne tolerira steroidov ali odziv ni zadosten
    - če ni odziva po 2-4 tednih visokih odmerkov steroidov
    - če se ni vnetje umirilo po 1 mesecu visokih odmerkov steroidov
    - če je za vzdrževanje potrebno več kot 8mg metilprednizolona

Jabs DA et al. 2000
Marianne D. 2012
Huang JJ, Gaudio PA. 2012

Imunomodulatorna zdravila

skupina	tip agensa	snov	
kortikostroidi			
antimetaboliti	analogi folne kisline	metotrexat	Metotrexat
	analogi purinov	azatioprim	Imuran
	inhibitor inozin monofosfat dehidrogenaze	mikofenolat mofetil	Cellcept
alkilirajoče snovi		ciklofosfamid	Endoxan
		klorambucil	Leukeran
naravne snovi	antibiotiki	ciklosporin	Sandimmun
		takrolimus	Prograf

Kortikosteroidi

- glukokortikoidno in mineralokortikoidno delovanje

Corticosteroid	Relative Antiinflammatory Activity	Relative Mineralocorticoid Activity	Equivalent Dose (mg)	Plasma Half-life (min)
Cortisone	0.8	0.8	25	30
Hydrocortisone	1.0	1.0	20	90
Prednisone	4.0	0.8	5	60
Prednisolone	4.0	0.8	5	200
Triamcinolone	5.0	0.0	4.0	300
Methylprednisolone	5.0	0.0	4.0	180
Betamethasone	25.0	0.0	0.75	100–300
Dexamethasone	25–30	0.0	0.75	100–300
Fludrocortisone	10	125	—	200

Kwame A. 2007

Kortikosteroidi

Parameter	Suggested Guideline
Initial dose	1 mg/kg/day*
Maximum adult oral dose	60–80 mg/day
Maintenance dose (adult)	≤10 mg/day
Tapering schedule	Over 40 mg/day, decrease by 10 mg/day every 1–2 weeks
	40–20 mg/day, decrease by 5 mg/day every 1–2 weeks
	20–10 mg/day, decrease by 2.5 mg/day every 1–2 weeks
	10–0 mg/day, decrease by 1 to 2.5 mg/day every 1–4 weeks
Monitor	Blood pressure, weight, glucose every 3 months
	Lipids (cholesterol and triglycerides) annually
	Bone density within first 3 months and annually thereafter
Supplemental treatment	Calcium 1500 mg daily and vitamin D 800 IU daily
	Estrogens and antiresorpative agents as needed

*In selected situations, where an immediate effect is needed, some investigators will begin with intravenous methylprednisolone at a dosage of 1 gm/day for 3 days and then start oral prednisone.

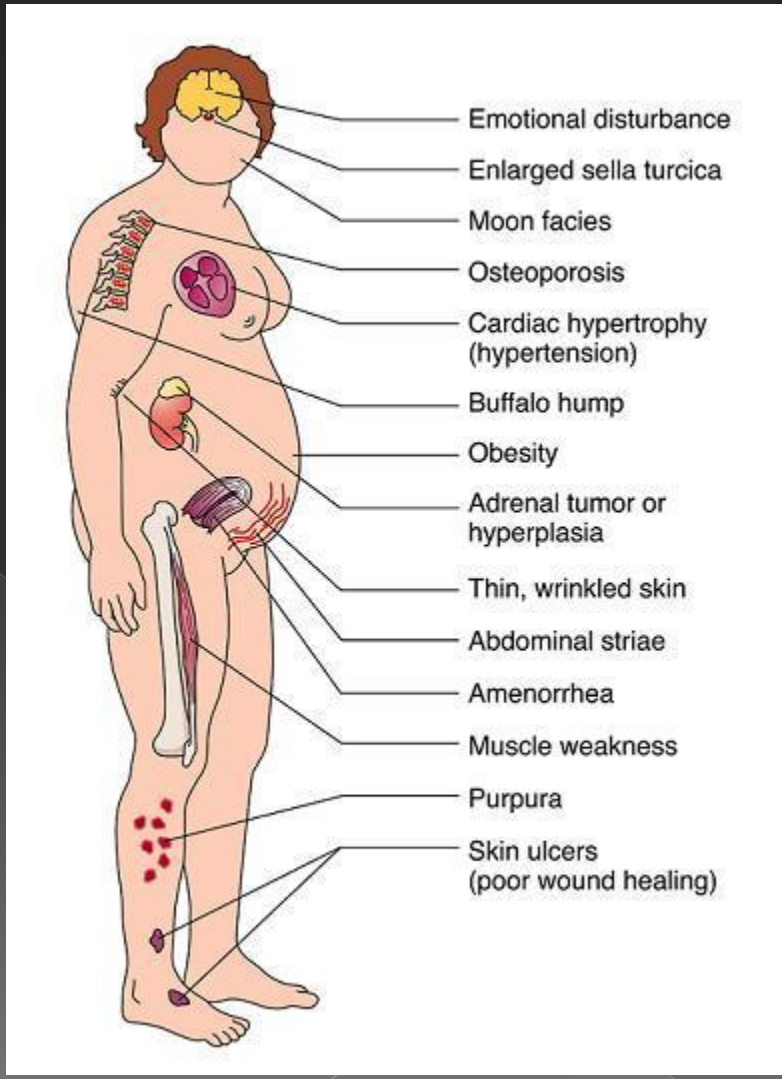
5mg prednizolona = 4mg metilprednizolona

V tujini se uporablja prednizolon, pri nas metilprednizolon (Medrol).

Douglas et al. 2000

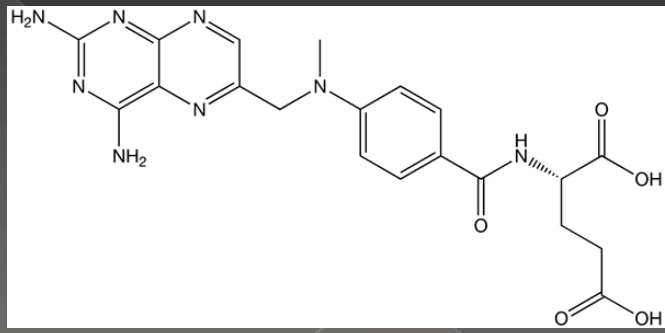
Stranski učinki kortikosteroidov

- osteoporoza
- debelost
- hiperglikemija
- atrofija kože
- strije
- okužbe
- aseptična kostna nekroza
- psihoza
- zastoj rasti pri otrocih



Metotreksat

- analog folata - inhibira dihidrofolat reduktazo
- doziranje: 7,5 - 25 mg 1x/teden
- stranski učinki:
  - supresija kostnega mozga
  - gastrointestinalne (GI) težave
  - hepatotoksičnost
  - neplodnost in teratogenost
  - metotreksatni pnevmonitis
  - NE živa cepiva



Jabs DA et al. 2000
Alex F, Joseba A. 2014
Parul S, Abhishek S. 2013

Metotreksat

- v 66% umiritev vnetja v 1 letu*
- ne povečuje celokupne smrtnosti in smtnosti zaradi rakavih obolenj

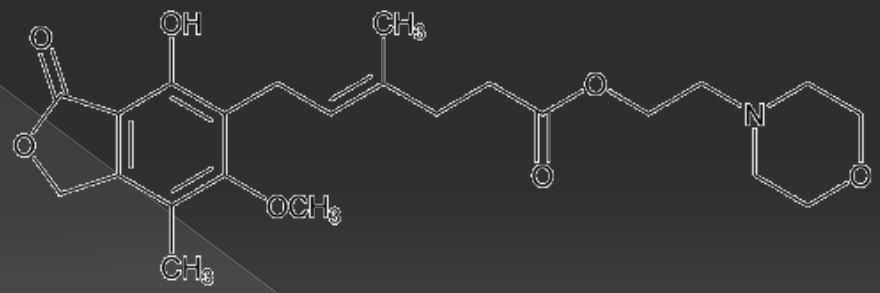
Drug	Typical Dose	PRE-TREATMENT	FBC	U&E Creat (1)	LFT	BP	URINE DipStick protein	FREQUENCY/COMMENT
Methotrexate (2) Folic Acid	7.5 - 25 mg ONCE a week. Increase every 2-6 weeks to maximum dose of 25mg ONCE weekly. Rarely max 30mg/week (See main text) 5 mg ONCE weekly ≥24 hours after Methotrexate	1.FBC, U&E, LFT , CXR (within the last 6 months) & 2.Pulmonary Function Test in selected patients.	√	√	√	–	–	FBC, U&E, LFT **every 2 weeks** until dose and monitoring **stable for 6 weeks**; thereafter **monthly**, until the dose and disease is stable for a year. Thereafter based on clinical judgement and following discussion with specialist team consider reducing frequency of monitoring **to every 2 - 3 months** Albumin – unexplained fall (in absence of active disease) – withhold and discuss New or increasing dyspnoea or dry cough – withhold and discuss urgently with the specialist team Avoid prescribing trimethoprim or cotrimoxazole to patients receiving methotrexate – greatly increases risk of marrow aplasia

FBC: full blood count, U&E: urea and electrolytes, LFT: liver function tests, BP: blood pressure, CXR: chest X-ray

*SITE - Systemic Immunosuppressive Therapy for Eye Disease
DMARD guideline group. 2009

Mikofenolat mofetil

- inhibira inozin monofosfat dehidrogenazo
  največji odmerek je 3g/dan
- Doziranje: 2x1000mg/dan
- stranski učinki:
  - supresija kostnega mozga
  - gastrointestinalne (GI) težave
  - hepatotoksičnost
  - NE živa cepiva



Jabs DA et al. 2000
Alex F, Joseba A. 2014
Parul S, Abhishek S. 2013

Mikofenolat mofetil

- v 73% umiritev vnetja v 1 letu*
- v 12% prenehali jemati po 1 letu zaradi stranskih učinkov*
- ne povečuje celokupne smrtnosti in smtnosti zaradi rakavih obolenj

Drug	Typical Dose	PRE-TREATMENT	FBC	U&E Creat (1)	LFT	BP	URINE DipStick protein	FREQUENCY/COMMENT
Mycophenolate Mofetil	Start 500mg daily increase **weekly** by 500mg to optimal or max. tolerated dose. Max - **3 gms /day**	FBC, U&E, LFT & CXR (within the last 6 months	√	–	–	–	–	FBC **weekly** until dose **stable for 4 weeks** then **fortnightly for 2 months.** **Monthly thereafter**, even after patient is stabilized on treatment.

FBC: full blood count, U&E: urea and electrolytes, LFT: liver function tests, BP: blood pressure, CXR: chest X-ray

DMARD guideline group. 2009

Azatioprin

- spremeni metabolizem purinov
- aktiven metabolit nastane v jetrih
- doziranje: 2 - 3 mg/kg/dan

pred uvedbo nujno preveriti aktivnost tiopurin metil-transferaze (TPMT)!

- v primeru jemanja alopurinola zmanjšati dozo za 25%
- stranski učinki:
  - supresija kostnega mozga
  - gastrointestinalne (GI) težave
  - hepatotoksičnost
  - hematotoksičnost
  - NE živa cepiva
  - nosečnost relativno kontraindicirana



Jabs DA et al. 2000
Alex F, Joseba A. 2014
Parul S, Abhishek S. 2013

Azatioprin

- v 62% umiritev vnetja v 1 letu*
- v 24% prenehali jemati po 230 dneh zaradi str. učinkov*
- ne povečuje celokupne smrtnosti in smtnosti zaradi rakavih obolenj

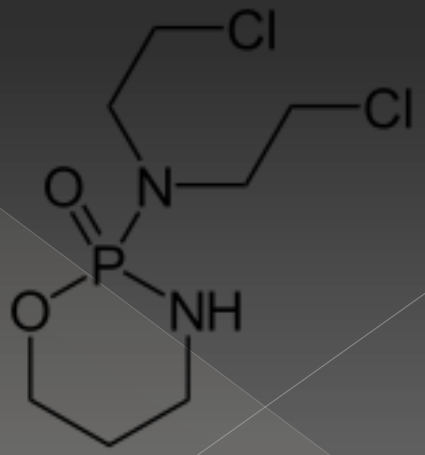
DRUG	TYPICAL DOSE	PRE-TREATMENT	FBC	U&E, Creat (1)	LFT	BP	URINE DipStick protein	FREQUENCY / COMMENT
Azathioprine	1mg/kg/day increase at 4-6 weekly intervals to **max** 3mg/kg/d	FBC, U&E, LFT, Creatinine, **TPMT assay**	√	√ SIX Monthly	√	–	–	FBC and LFT **weekly for 6 weeks** and then every **2 weeks** until dose stable for **6 weeks**; then **monthly**. After dose increase - repeat FBC and LFT's after **2 weeks** and then **monthly** If dose and test results stable for **6 months** consider discussing with patient to reducing to **3 monthly**. In patients **heterozygote** for TPMT, monitoring should continue at **monthly** intervals U&E, creatinine – **6 monthly**

FBC: full blood count, U&E: urea and electrolytes, LFT: liver function tests, BP: blood pressure

DMARD guideline group. 2009

Ciklofosfamid

- iregularno spajanje baz DNA
- aktiven metabolit nastane v jetrih
- doziranje: 1 - 3 mg/kg/dan
- stranski učinki:
  - supresija kostnega mozga
  - gastrointestinalne (GI) težave
  - hemoragični cistitis
  - sterilnost in teratogenost
  - NE živa cepiva



Jabs DA et al. 2000
Alex F, Joseba A. 2014
Parul S, Abhishek S. 2013

Ciklofosfamid

- v 76% nadzor vnetja v 1 letu*
- v 33,5% prenehali jemati po 1 letu zaradi str. učinkov*
- ne povečuje celokupne smrtnosti, verjetnost smrti zaradi malignega obolenja je nesignifikantno povečana.

DRUG	TYPICAL DOSE	PRE-TREATMENT	FBC	U&E, Creat	LFT	BP	URINE DipStick Protein	FREQUENCY / COMMENT
Cyclophosphamide	1-3mg/kg/dan	FBC, U&E, Creatinine, Urine	√	√	√	√	√	FBC, U&E and Creatinine every 2 weeks Urinalysis monthly

FBC: full blood count, U&E: urea and electrolytes, LFT: liver function tests, BP: blood pressure

DMARD guideline group. 2009

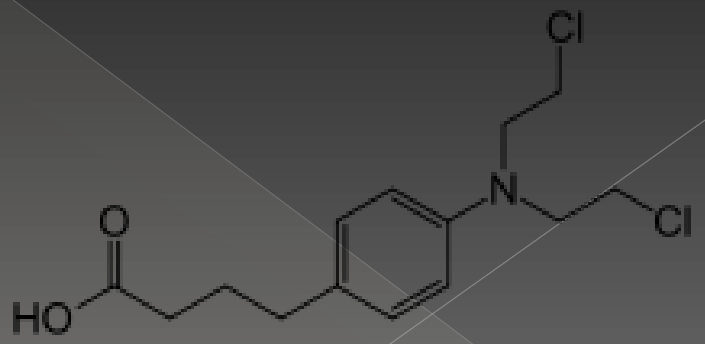
Klorambucil

- iregularno spajanje baz DNA

titriranje na 3 tedne, maksimalna doza 12mg/dan nato zmanjševanje v 6 mesecih

- doziranje: 0,1 mg/kg/dan

- stranski učinki:
  - supresija kostnega mozga
  - sterilnost
  - pljučna fibroza
  - NE živa cepiva



Jabs DA et al. 2000
Alex F, Joseba A. 2014
Parul S, Abhishek S. 2013

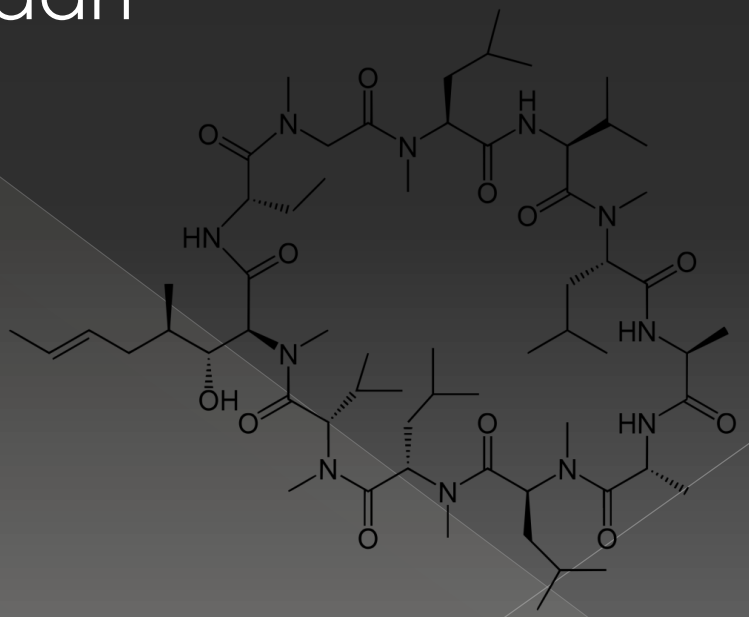
Klorambucil

- majhen vzorec pacientov s klorambucilom
- ne povečuje celokupne smrtnosti, verjetnost smrti zaradi malignega obolenja je nesignifikantno povečana
- kontrola KKS in DKS vsak teden

KKS: celotna krvna slika, DKS: diferencialna krvna slika

Ciklosporin

- inhibicija aktivacije NF-AT
- doziranje: 2,5 - 5 mg/kg/dan
- stranski učinki:
  - supresija kostnega mozga
  - GI motnje
  - nefrotoksičnost
  - nevrotoksičnost - tremor
  - NE živa cepiva



Jabs DA et al. 2000
Alex F, Joseba A. 2014
Parul S, Abhishek S. 2013

Ciklosporin

- v 52% nadzor vnetja v 1 letu*
- v 10,7% prenehali jemati po 1 letu zaradi str. učinkov*
- ne povečuje celokupne smrtnosti in smtnosti zaradi rakavih obolenj

DRUG	TYPICAL DOSE	PRE-TREATMENT	FBC	U&E, Creat (1)	LFT	BP	URINE DipStick protein	FREQUENCY / COMMENT
Ciclosporin	Start 2.5mg/kg/day in two divided doses for 6 weeks and then may be incrementally increased by 25mg at 2–4 weekly intervals until clinically effective or the maximum dose of 4mg/kg is reached	FBC, U&E, LFTCreatinine: Twice at 2 week apart – to obtain mean value Creatinine clearance or equivalent Fasting Lipids BP: ≤140/90 on 2 occasions at 2/52 apart.	√	√	√	√	–	U & E including potassium and Creatinine **every 2 wks** until dose and results stable for **3 months** and then **monthly** FBC and LFT **monthly** until dose and results stable for **3 months; thereafter 3 monthly.** Vigilance when NSAID added **particularly diclofenac**- reduce **diclofenac dose** by 50% Blood pressure monitoring each attendance. BP > 140/90 on 2 consecutive readings 2/52 apart – treat hypertension before stopping ciclosporin (Note possible drug interactions). If BP cannot controlled, stop ciclosporin and obtain BP control before restarting ciclosporin Check fasting **lipids periodically**

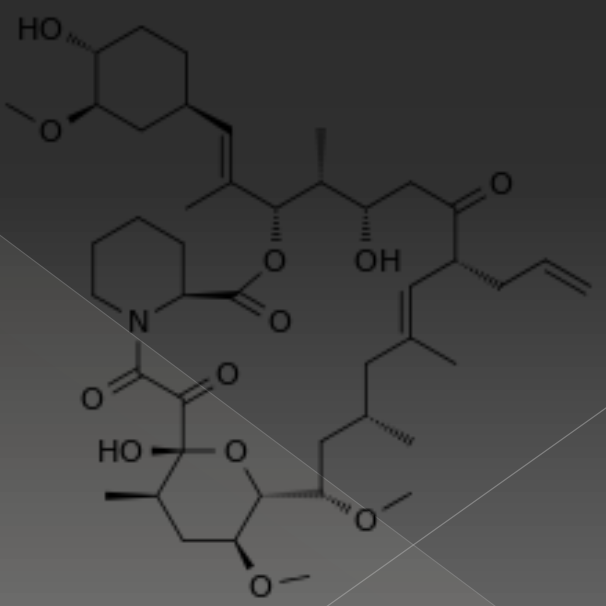
nekateri avtorji svetujejo tudi odvzeme urina na 2 meseca

FBC: full blood count, U&E: urea and electrolytes, LFT: liver function tests, BP: blood pressure

DMARD guideline group. 2009

Takrolimus

- inhibicija aktivacije NF-AT
- doziranje: 0,05 mg/kg/dan
- stranski učinki:
  - supresija kostnega mozga
  - nefrotoksičnost
  - nevropatije
  - hipertenzija
  - NE živa cepiva



Jabs DA et al. 2000
Alex F, Joseba A. 2014
Parul S, Abhishek S. 2013

Takrolimus

- spremljanje kot pri ciklosporinu
- spremljanje koncentracije zdravila zaradi spremenljive absorbcije

Povzetek SITE študije

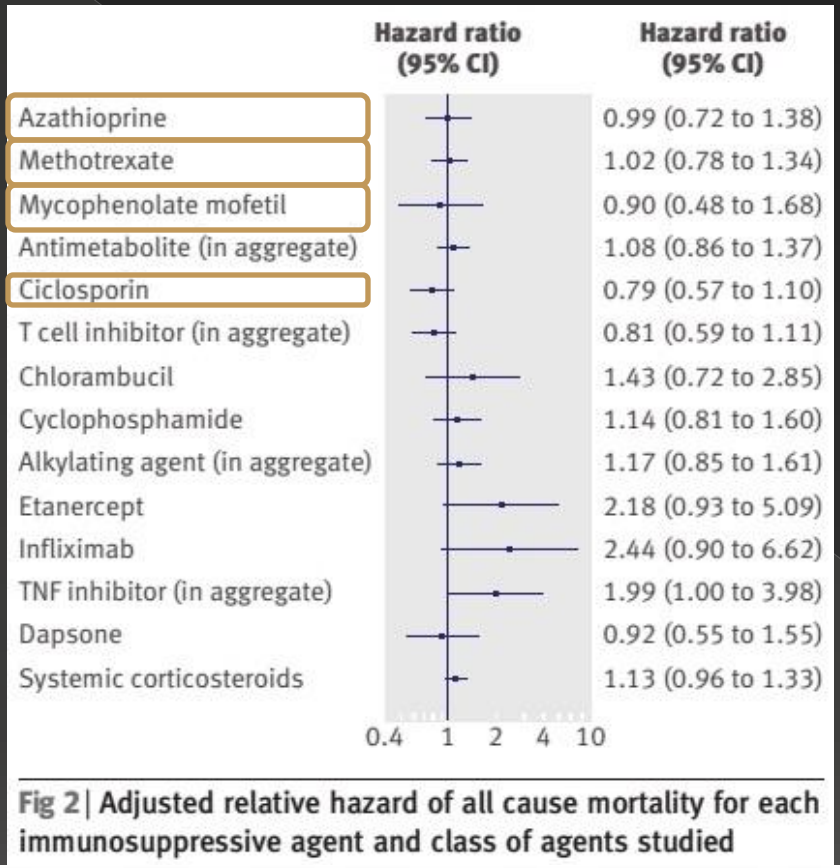


Fig 2 | Adjusted relative hazard of all cause mortality for each immunosuppressive agent and class of agents studied

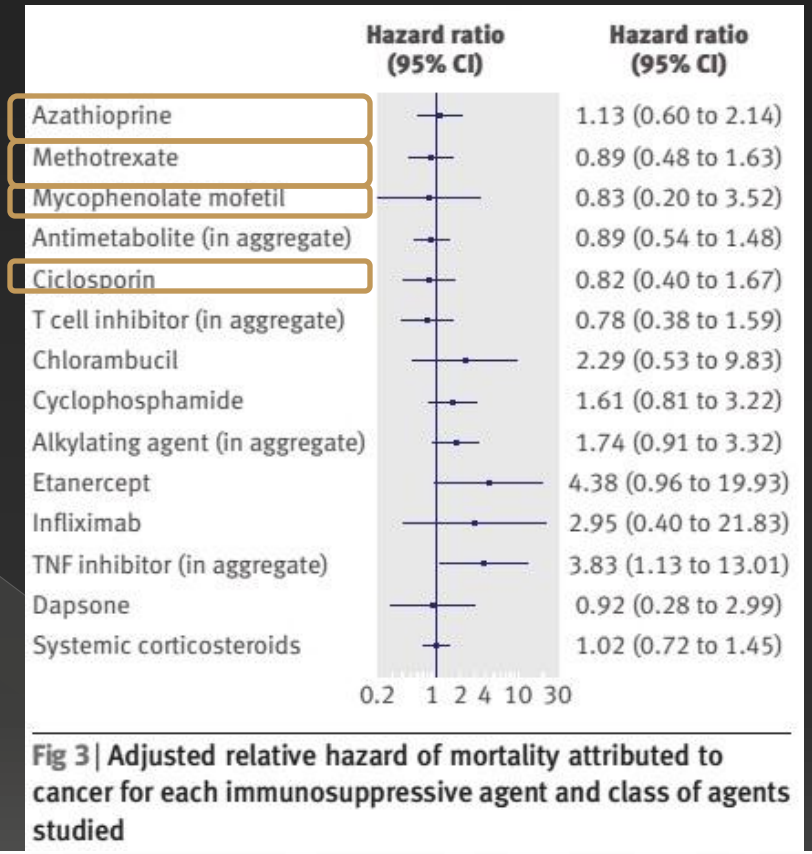


Fig 3 | Adjusted relative hazard of mortality attributed to cancer for each immunosuppressive agent and class of agents studied

Table 2 | Risk of overall and cancer mortality in cohort compared with 1999-2005 US general population, standardised for age, race, and sex

Use of immuno-suppressive agents	Number of patients	Median follow-up time	Observed deaths	Total person time	Indirectly standardised mortality rate per 100 person years	Standardised mortality ratio (95% CI)	Cancer deaths	Indirectly standardised cancer mortality rate per 100 person years	Standardised cancer mortality ratio (95% CI)
None	6545	5.68	562	46086	0.89	1.02 (0.94 to 1.11)	149	0.22	1.10 (0.93 to 1.29)
Any	2285	5.60	321	17006	0.91	1.04 (0.93 to 1.16)	69	0.20	1.03 (0.80 to 1.31)
Total	7628	6.98	883	63079	0.90	1.03 (0.96 to 1.10)	218	0.22	1.07 (0.94 to 1.23)

Totals are less than sum of treatment categories because some patients received more than one treatment. Total number of patients excludes 329 patients for whom age, race, or sex (predominantly race) information was missing. Observed deaths and total person time are slightly lower than in table 1 because of exclusion of patients for whom age, race, or sex were missing for standardised mortality ratio calculations.

Spremljanje laboratorijskih vrednosti za stranske učinke

IMT	Pred zdravljenjem	Pogostost spremljanja za stranske učinke
Metotrexat	KSK, U&E, jetrni encimi, Rtg PC, testi pljučne funkcije	KKS, U&E, jetrni encimi 1x/2 tedna, če stabilno 6 tednov 1x/mesec, če stabilno 1 leto 1x/3 mesece Prekiniti če poslabšana dispneja, suh kašelj, padec albuminov. Ne skupaj s TMP.
Mikofenolat mofetil	KKS, U&E, jetrni encimi, Rtg PC	KKS 1x/teden, če stabilno 4 tedne 1x/2 tedna 2 meseca, nato 1x/mesec
Azatioprin	KKS, U& E, kreatinin, jetrni encimi TPMP	KKS in jetrni encimi 1x/teden prvih 6 tednov, 1x/2 tedna nadaljnih 6 tednov, nato 1x/mesec, če stabilno na 3 mesece heterozgoti za TPMP 1x/mesec U&E in kreatinin 1x/6 mesecev
Ciklosporin	KKS, U&E, kreatinin, lipidogram, krvni pritisk <140/90mmHg	U&E in kreatinin 1x/2 tedna, če stabilno 3 mesece 1x/mesec KKS in jetrni encimi 1x/mesec, če stabilno 3 mesece 1x/3 mesece RR ob vsakem obisku Lipidogram 1x/leto
Ciklofosfamid	KKS, U&E, k reatinin, jetrni encimi, urin	KKS, U&E in kreatinin 1x/2 tedna. Analiza urina 1x/mesec
Klorambucil	KKS, DKS	KKS in DKS 1x/teden
Takrolimus	KKS, U&E, kreatinin, lipidogram, krvni pritisk <140/90mmHg	U&E in kreatinin 1x/2 tedna, če stabilno 3 mesece 1x/mesec KKS in jetrni encimi 1x/mesec, če stabilno 3 mesece 1x/3 mesece RR ob vsakem obisku Lipidogram 1x/leto Spremljanje nivoja zdravila v krvi

KKS: celotna krvna slika, U&E: urea in elektroliti, Rtg PC: rentgenogram pljuč, DKS: diferencialna krvna slika, RR: krvni pritisk

Povzeto po DMARD guideline group. 2009

Povzetek

- Kortikosteroidi naj se uporabljajo v akutni fazi v visokih dozah
- Kolikor so potrebni vzdrževalni odmerki nad 8 mg Medrola/dan je potrebna uvedba IMT
- Čas jemanja IMT je okvirno 18 - 24 mesecev
- **Klasični IMT ne povečujejo smrtnosti in obolevnosti za rakom in so varna ob ustreznem spremljanju stranskih učinkov pri osebnem zdravniku***
  - z izjemo alkilirajočih snovi, ki nesignifikantn povečajo celokupno smrtnost in smrtnost zaradi raka

Prikaz primera

- 20-letna pacientka
- **obojestranski kronični granulomatozni panuveitis**
- brez pridruženih revmatskih obolenj
- alergija na gluten
- obsežna diagnostika: kvantiferonski test, serologija na Toxocaro, Toxoplasmo, Leptospiro, Borelijo lajmske borelioze, ANA, ANCA, katepsin, elastaza, laktoferin, lizocim, HSV, S-ACE, Rtg PC so bili negativni
- **HLA B51 +**

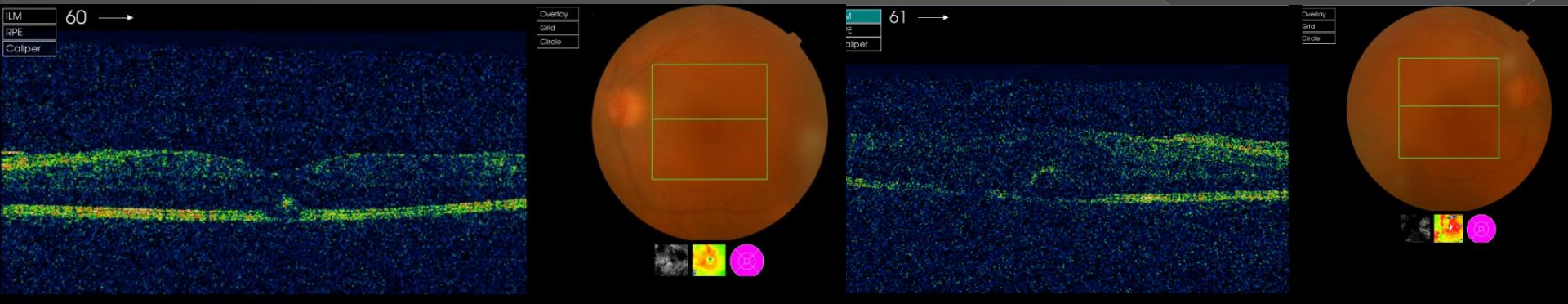
Potek zdravljenja

2009

- Uveden Medrol 40mg/dan s postopnim nižanjem
- Vzdrževalna doza 2/8mg izmenično
  - Topična terapija

Stanje ob hospitalizaciji:
Vdo: 0,1 s.c.
Vlo: 0,3 s.c
Doko: cc 1+, v steklovini 2-3+
Loko: cc 1+, v steklovini 2-3+

Stanje po uvedbi steroida:
Vdo: 0,6 s.c.
Vlo: 0,6p s.c
Doko: cc +/-, v steklovini 2+
Loko: cc +/-, v steklovini 1+

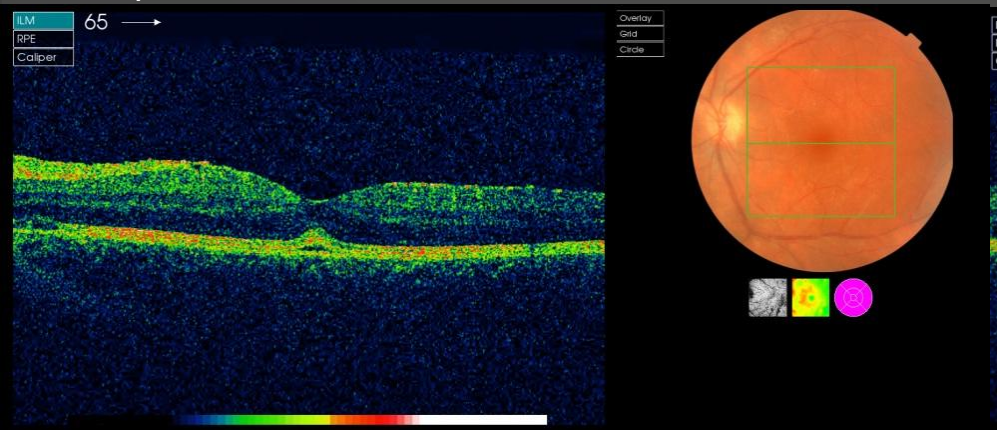


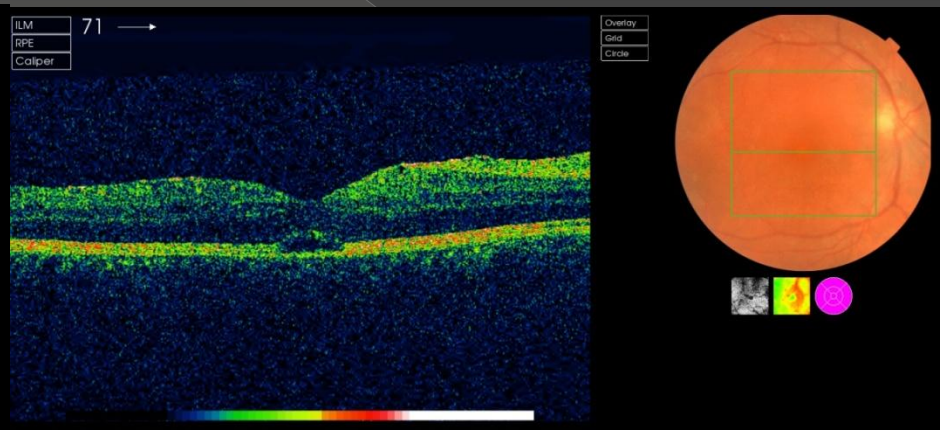
2010

- Medrol 64mg 3dni nato nižanje
- uveden **Metotrexat** 12,5mg na teden
- Folacin 5mg na teden

Stanje ob hospitalizaciji:
Vdo: 0,3 s.c.
Vlo: 0,7 s.c.
Doko: cc 2+
Loko: cc 1+

OCT po uvedbi Metotrexata

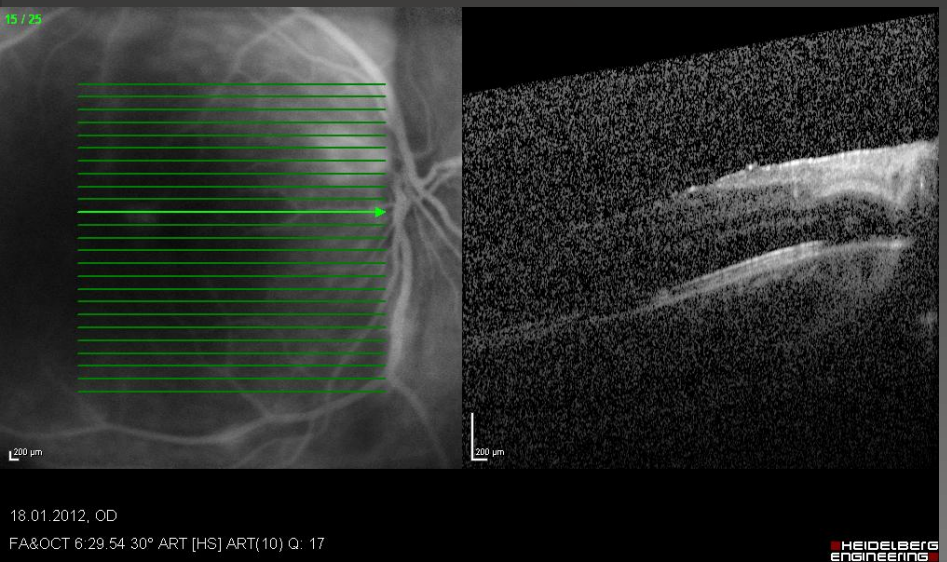


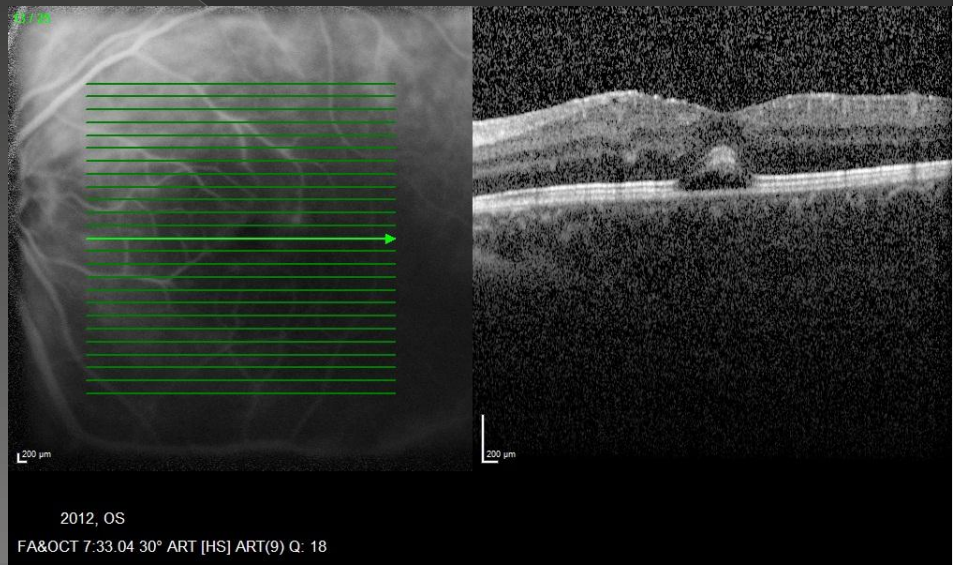


2012

- Medrol 2mg/8mg izmenično
- Metotrexat 15mg na teden
- Folacin 5mg na teden

Stanje ob hospitalizaciji:
Vdo: 0,5 s.c.
Vlo: 0,6 s.c
Doko: cc +/-
Loko: cc 1+

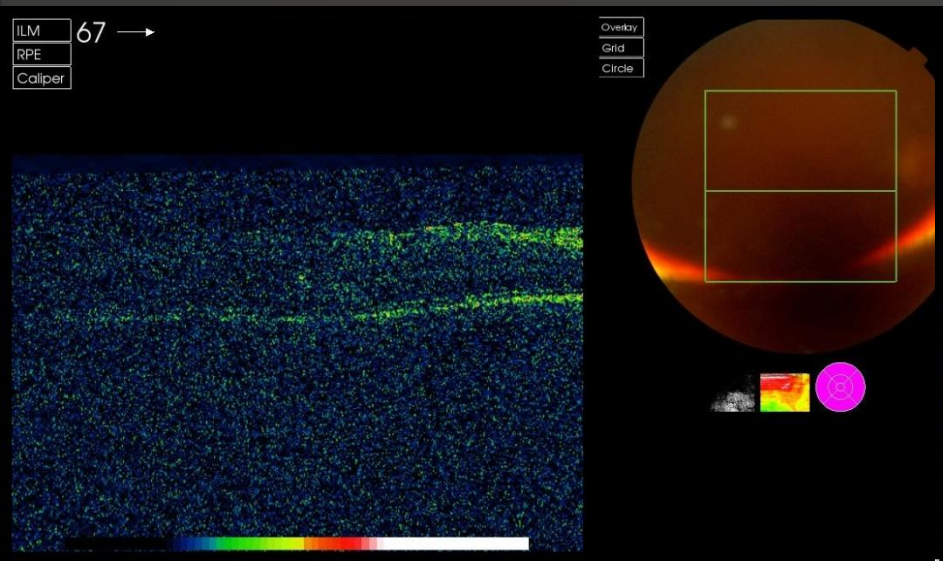


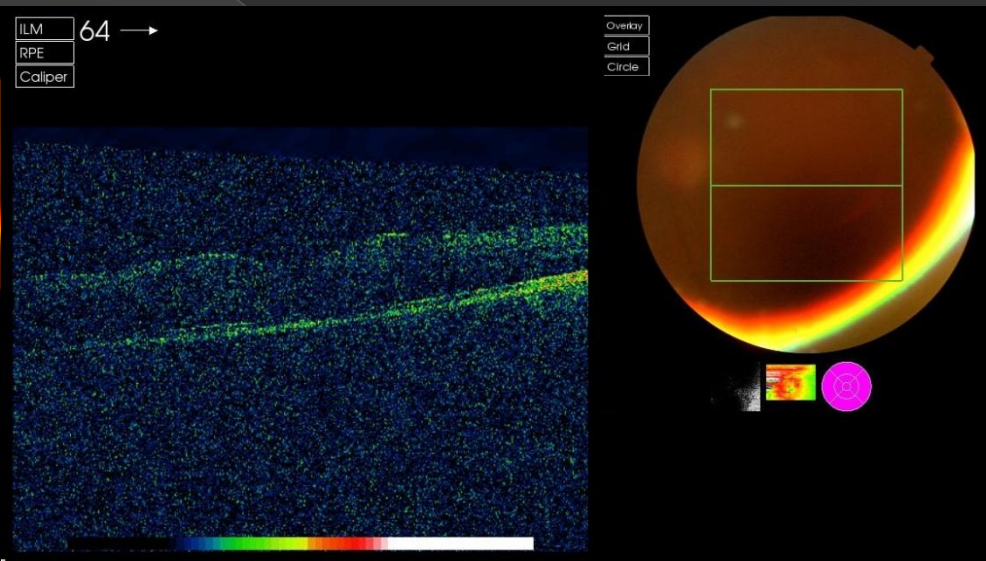


2012

- Medrol 2mg/8mg izmenično
- Metotrexat ex.
- **Mikofenolat mofetil** 4x500mg/dan
- Vnetje ves čas slabo nadzorovano, pri zadnjih obiskih več makularnega edema obojestransko

Stanje ob obisku:
Vdo: 0,4p s.c.=c.c.
Vlo: 06p c.c.
Doko: brez eksudacije
Loko: brez eksudacije

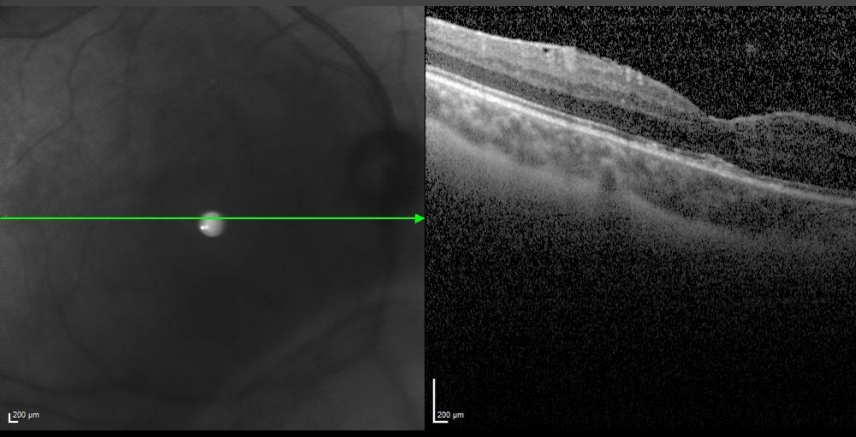


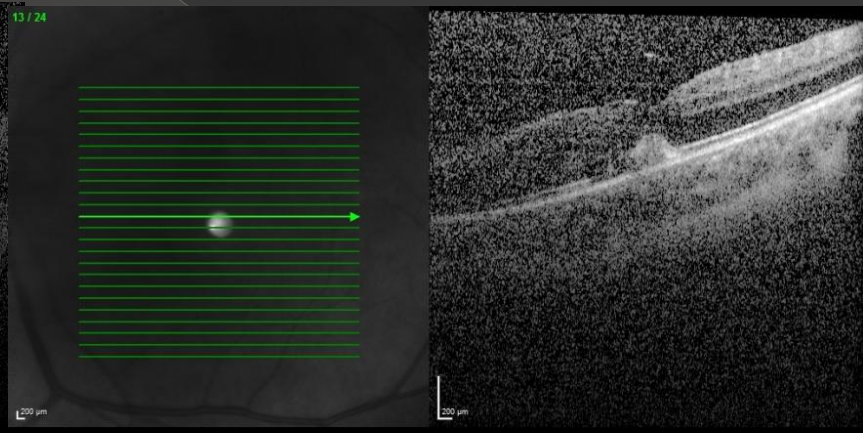


2013

- Medrol 2mg/8mg izmenično
- Mikofenolat mofetil ex.
- **Azatioprin** 3x50mg/dan
- **Ciklosporin** 250mg/dan
- Vid stalno peša, ponovno nekoliko boleči, rdeči očesi

Stanje ob hospitalizaciji:
Vdo: 0,2 s.c.=c.c.
Vlo: 0,5 s.c.=c.c.
Doko: brez eksudacije
Loko: brez eksudacije



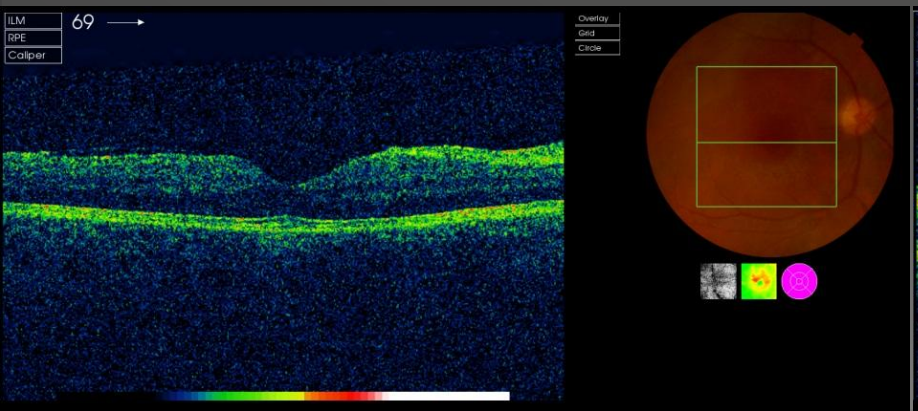


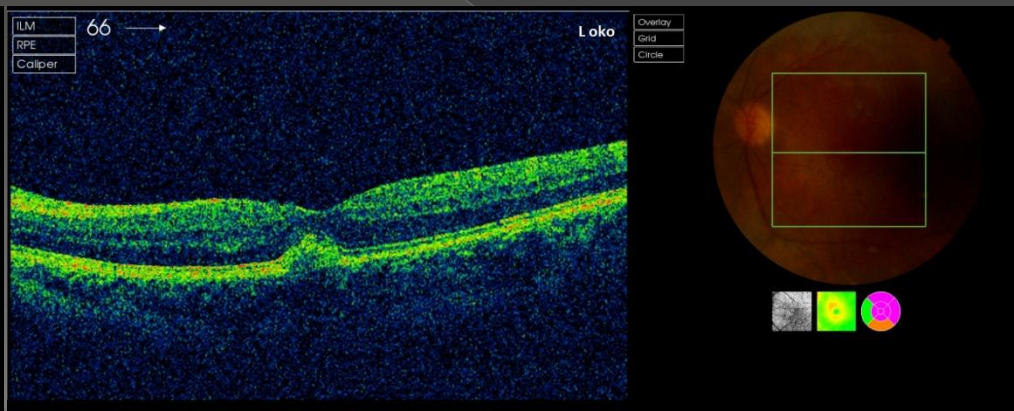
2014

- op. sive mrene desno, nato levo
- Medrol 4mg/dan
- Azatioprin 3x50mg/dan
- Ciklosporin 21750mg/dan
  - Topična terapija

Stanje ob zadnjem obisku:
Vdo: 1,0 s.c.
Vlo: 0,8 c.c.
Doko: v prekatu c+/-, v steklovini 1–2+
Loko: v prekatu 1+, v steklovini 1+

OCT po op. sive mrene desno in levo





Hvala za pozornost

