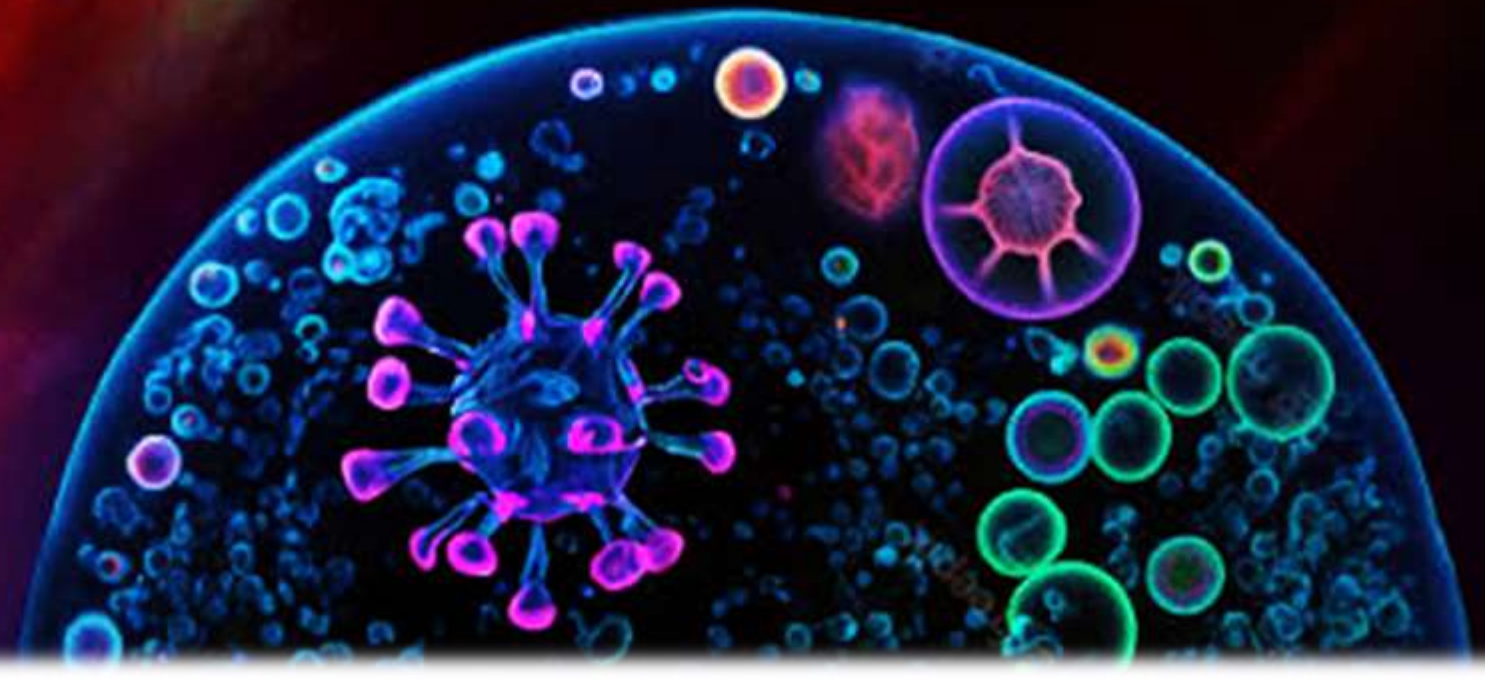
I. VİRAL İNFEKSİYONLAR VE BAĞIŞIKLAMA SİMPOZYUMU



KRONİK HEPATİT B VE YAN ETKİ YÖNETİMİ

OLGU SUNUMU

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Gastroenteroloji Kliniği

- 39 yaş kadın hasta
- 15 yıldır HBV tanılı
- Varis kanaması sonrası kronik HBV' ye sekonder KC-S tanısı
- 22 hafta önce karaciğer transplantasyonu

- Nakilden önceki 3 ay boyunca
- Lökosit sayısı 1,6 ile 3,3 × 10 9 /L arasında
- Mutlak nötrofil sayısı 0,6 ile 1,9 × 10 9 /L arasında

WBC	Onaylandı	1,75	✓	10^9/L	4,49	12,68
RBC	Onaylandı	3,21	✓	10^12/L	3,92	5,08
HGB	Onaylandı	10,5	✓	g/dL	10,6	13,5
HCT	Onaylandı	32,6	✓	%	36,6	44
MCV	Onaylandı	101,6	✓	fL	77,7	93,7
MCHC	Onaylandı	32,2	✓	g/dL	31	34,1
PLT	Onaylandı	34	✓	10^9/L	150	400
MPV	Onaylandı	----	✓	fL	9,1	11,9
PCT	Onaylandı	----	✓	%	0,18	0,39
PDW	Onaylandı	----	✓	fL	9,8	16
NEU#	Onaylandı	1,04	✓	10^9/L	2,1	8,89
LYM#	Onaylandı	0,51	✓	10^9/L	1,26	3,35
MON#	Onaylandı	0,18	✓	10^9/L	0,25	0,84
EOS#	Onaylandı	0,01	✓	10^9/L	0,01	0,4
BAS#	Onaylandı	0,01	✓	10^9/L	0,01	0,07
NEU%	Onaylandı	59,4	✓	%	42,9	74,3
LYM%	Onaylandı	29,1	✓	%	18,3	45,7
MON%	Onaylandı	10,3	✓	%	4,2	11,8
EOS%	Onaylandı	0,6	✓	%	0,2	5,3
BAS%	Onaylandı	0,6	✓	%	0,1	1
RDW-CV	Onaylandı	15,8	✓	%	12,4	15,1

- Nakilden sonraki 4 ila 21 hafta arasında
- Lökosit sayısı 1,9 ile 6,5 × 10 9 /L arasında
- Nötrofil 1,2 ile 3,4 × 10 9 /L arasında değişti.

- Anizositoz
- Poikilositoz
- Belirgin hipokromik mikrositer eritrositler
- Lenfositler nispeten artmıştı
- Nötrofiller azalmıştı
- Atipik hücre saptanmamıştı

- Hastada nakilden 22 hafta sonra önemli nötropeni gelişti; Mutlak nötrofil sayısı 0,8 × 10 9 /L idi
- Granülosit-koloni uyarıcı faktör (G-CSF) uygulandı; hem asiklovir hem de TMP/SMX kesildi.
- Sitomegalovirüs (CMV) ve Ebstein-Barr virüsü (EBV) için PCR sonuçları negatifti.
- HBV nüksetmesine dair laboratuvar kanıtı yoktu
- Beslenme eksikliği bulgusu yoktu

Kullandığı ilaçlar

- Prograf
- Deltacortil
- Asiklovir
- Bactrim
- Entekavir

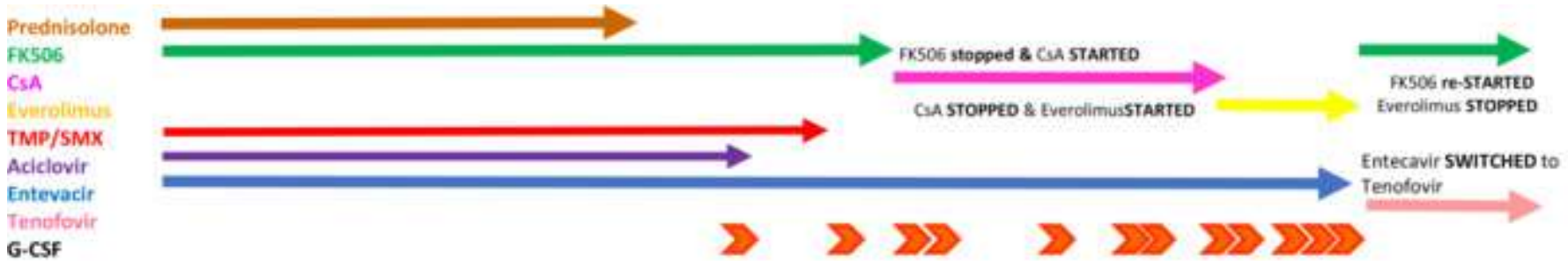
Major medications with a definite association with agranulocytosis

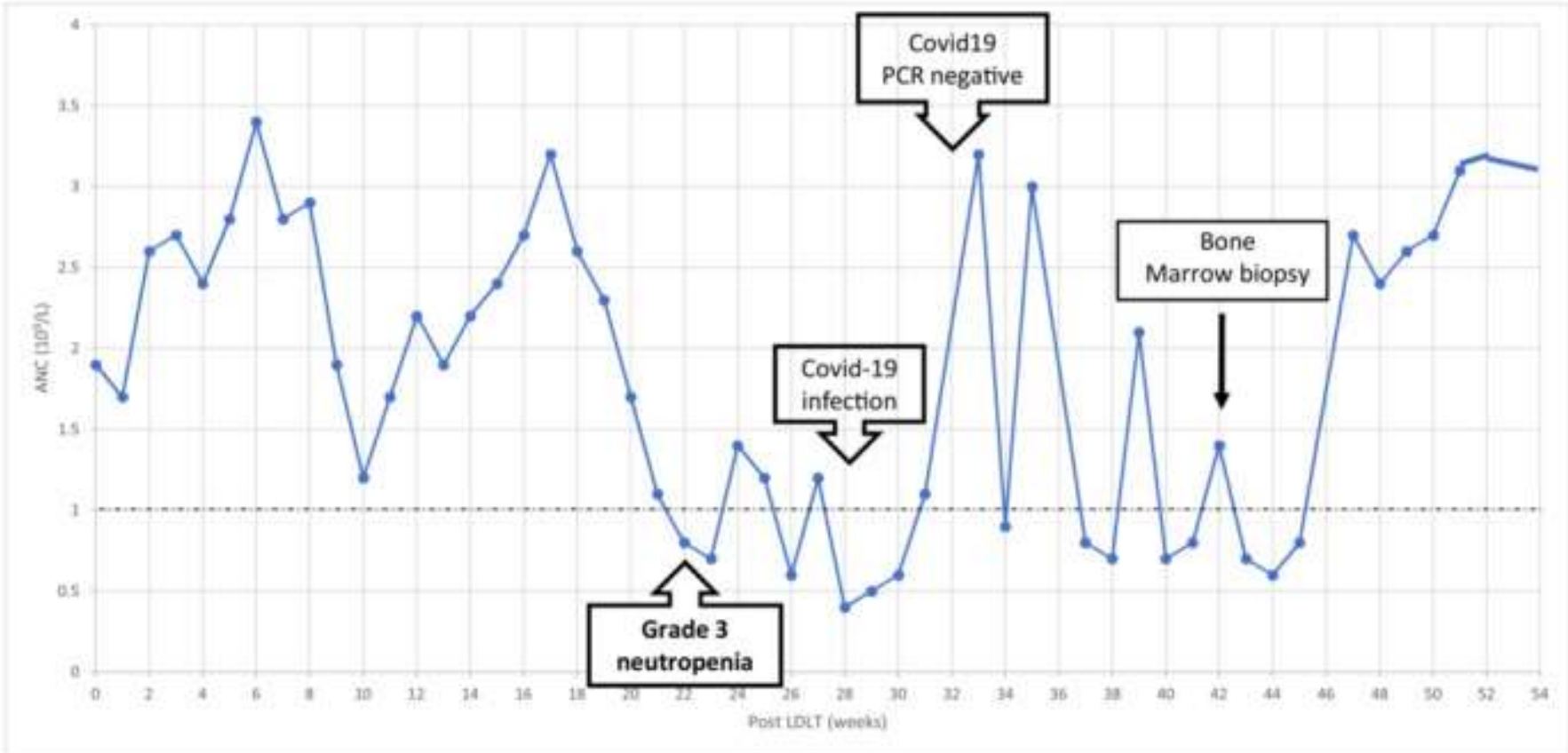
Antithyroid drugs (thionamides)
Methimazole
Carbimazole
Propylthiouracil
Anti-inflammatory drugs
Sulfasalazine
Nonsteroidal anti-inflammatory drugs
Gold salts
Leflunomide
Methotrexate
Penicillamine
Phenylbutazone
Antipyrine
Dipyrone
Phenacetin
Psychotropic drugs
Clozapine
Phenothiazines
Tricyclic and tetracyclic antidepressants
Meprobamate
Cocaine/heroin (adulterated with levamisole)
Gastrointestinal drugs
Sulfasalazine
Histamine type 2 receptor antagonists
Cardiovascular drugs
Antiarrhythmic agents (tocainide, procainamide, flecainide)
Ticlopidine
ACE inhibitors (enalapril, captopril)
Propranolol
Dipyridamole
Digoxin
Dermatologic drugs
Dapsone
Isotretinoin
Miscellaneous
Chlorpheniramine

Antibiotics
Macrolides
Trimethoprim-sulfamethoxazole
Chloramphenicol
Sulfonamides
Semisynthetic penicillins
Vancomycin
Cephalosporins
Dapsone
Antimalarial drugs
Amodiaquine
Chloroquine
Hydroxychloroquine
Quinine
Antifungal agents
Amphotericin B
Flucytosine
Antiviral agents
Oseltamivir
Ganciclovir
Acyclovir
Antiseizure medications
Carbamazepine
Phenytoin
Ethosuximide
Valproate
Diuretics
Thiazides
Acetazolamide
Furosemide
Spironolactone
Sulfonylureas
Chlorpropamide
Tolbutamide
Iron chelating agents
Deferiprone

- Nakilden 28 hafta sonra, kötüleşen nötropeni ve ilaçla ilişkili nötropeni şüphesi nedeniyle; İmmünsüpresyonun birincil seçeneği olan takrolimus durduruldu ve siklosporin (CsA) ile değiştirildi.

- Transplantasyondan sonraki 40. haftaya kadar CsA monoterapisine devam edildi ancak hirsutizm ve olası kalsinörin inhibitörü (CNI) kaynaklı nötropeni nedeniyle durduruldu ve everolimus başlandı.


Prednisolone
FK506
CsA
Everolimus
TMP/SMX
Aciclovir
Entevacir
Tenofovir
G-CSF
FK506 stopped & CsA STARTED
CsA STOPPED & EverolimusSTARTED
FK506 re-STARTED
Everolimus STOPPED
Entecavir SWITCHED to Tenofovir


Covid19
PCR negative
Bone
Marrow biopsy
Covid-19
infection
Grade 3
neutropenia
ANC (10⁹/L)
Post LDLT (weeks)

- Zamanla, G-CSF'nin giderek daha sık dozlarına ihtiyaç duydu
- Mutlak nötrofil sayısında nispeten daha küçük artışlarla sonuçlandı

- Manyetik rezonans portografisi planlandı
- Hastanın trombosit sayısı nakilden sonra 20-50 × 10 9 /L aralığından 50-100 × 10 9 /L aralığına yükselmişti
- Bu sayede nötropeni nedeni olarak rezidüel veya tekrarlayan hipersplenizm dışlanmıştı.

- Tüm potansiyel ilaç suçlularının kesilmesiyle birlikte, ETV 0,5 mg'ın günde bir kez, tenofovir alafenamid 25 mg ile değiştirildiği son bir değişiklik yapıldı
- Mutlak nötrofil sayısı ETV'nin kesilmesinden sonraki 2 hafta içinde iyileşti ve 6 aylık takipten sonra normal kaldı.

WBC	Onaylandı	4.54	✓	10^9/L	4,49	12,68
RBC	Onaylandı	4.44	✓	10^12/L	3,92	5,08
HGB	Onaylandı	10.9	✓	g/dL	10,6	13,5
HCT	Onaylandı	35.5	✓	%	36,6	44
MCV	Onaylandı	80	✓	fL	77,7	93,7
MCHC	Onaylandı	30.7	✓	g/dL	31	34,1
PLT	Onaylandı	139	✓	10^9/L	150	400
MPV	Onaylandı	----	✓	fL	9,1	11,9
PCT	Onaylandı	----	✓	%	0,18	0,39
PDW	Onaylandı	----	✓	fL	9,8	16
NEU#	Onaylandı	2,8	✓	10^9/L	2,1	8,89
LYM#	Onaylandı	1,28	✓	10^9/L	1,26	3,35
MON#	Onaylandı	0,42	✓	10^9/L	0,25	0,84
EOS#	Onaylandı	0,02	✓	10^9/L	0,01	0,4
BAS#	Onaylandı	0,02	✓	10^9/L	0,01	0,07
NEU%	Onaylandı	61.7	✓	%	42,9	74,3
LYM%	Onaylandı	28.2	✓	%	18,3	45,7
MON%	Onaylandı	9.3	✓	%	4,2	11,8
EOS%	Onaylandı	0.4	✓	%	0,2	5,3
BAS%	Onaylandı	0.4	✓	%	0,1	1

>10%: Hepatic: Increased serum alanine aminotransferase (>5 x ULN: 11% to 12%; >10 x ULN and >2 x baseline: 2%)

1% to 10%:

Dermatologic: Skin rash (children and adolescents: >1%)

Endocrine & metabolic: Glycosuria (4%), hyperglycemia (2% to 3%)

Gastrointestinal: Abdominal pain (children and adolescents: >1%), diarrhea (children and adolescents: >1%; adults: ≤1%), dyspepsia (≤1%), increased serum lipase (7%), nausea (children and adolescents: >1%; adults: <1%), vomiting (children and adolescents: >1%; adults: <1%)

Genitourinary: Hematuria (9%)

Hepatic: Increased serum bilirubin (2% to 3%)

Nervous system: Fatigue (1% to 3%), headache (2% to 4%)

Renal: Increased serum creatinine (1% to 2%)

<1%:

Endocrine & metabolic: Decreased serum albumin

Hematologic & oncologic: Thrombocytopenia

Nervous system: Dizziness, drowsiness, insomnia

In the clinical trials entecavir treatment was discontinued if patients achieved a prespecified resp
If treatment is discontinued without regard to treatment response, the rate of post-treatment ALT
could be higher.

d. Paediatric Population

The safety of entecavir in paediatric patients from 2 to < 18 years of age is based on two clinica
in subjects with chronic HBV infection; one Phase 2 pharmacokinetic trial (study 028) and one
Phase 3 trial (study 189). These trials provide experience in 195 HBeAg-positive nucleoside-
treatment-naïve subjects treated with entecavir for a median duration of 99 weeks. The adverse
reactions observed in paediatric subjects who received treatment with entecavir were consistent
those observed in clinical trials of entecavir in adults.(see a. Summary of the safety profile and
section 5.1) with the following exception in the paediatric patients:

- very common adverse reactions: neutropenia.

EUROPEAN UNION (EU) RISK MANAGEMENT PLAN (RMP) FOR ENTECAVIR (ETV)

RMP version to be assessed as part of this application:

Version Number: 15.0

Data-lock Point for this RMP: 23-Jul-2019

Date of Final Sign-off: 04-Nov-2019

Rationale for submitting an updated RMP: To reflect the removal of long-term safety and clinical outcomes, use in the paediatric population (from birth to less than 2 years of age), and use in elderly patients (≥ 65 years of age) as missing information. In addition, the Marketing Authorisation Holder (MAH) has reformatted the RMP in accordance with the revised guideline on Good Pharmacovigilance Practices (GVP) Module V (Rev 2).[1]

Summary of Significant Changes in This RMP

Part/Module	Summary of Major Changes	Version #/Date of Positive Opinion for Module Update
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	Not applicable (N/A)	Version 10.0/28-Oct-2013
SII Nonclinical part of the safety specification	Updated with information on Study AI463080 in regards to the risk of malignant neoplasms.	Version 15.0/Pending
SIII Clinical trial exposure	N/A	Version 14.0/25-Oct-2017
SIV Populations not studied in clinical trials	N/A	Version 13.0/18-Mar-2015
SV Post-authorisation experience	Updated post-authorisation exposure figures.	Version 15.0/Pending
SVI Additional EU requirements for the safety specification	N/A	Version 14.0/25-Oct-2017
SVII Identified and potential risks	Long-term safety and clinical outcomes, use in the paediatric population (from birth to less than 2 years of age), and use in elderly patients (≥ 65 years of age) removed as missing information.	Version 15.0/Pending
SVIII Summary of the safety concerns	Updated to reflect changes in SVII.	Version 15.0/Pending
Part III Pharmacovigilance Plan	N/A	Version 14.0/25-Oct-2017
Part IV Plan for Post-authorisation Efficacy Studies	N/A	Version 14.0/25-Oct-2017
Part V Risk-minimisation Measures	Long-term safety and clinical outcomes, use in the paediatric population (from birth to less than	Version 15.0/Pending

TABLE I

Adverse Drug Reaction Probability Scale (Naranjo)[9]

Question	Yes	No	Do Not Know	Score
1.Are there previous conclusive reports on this reaction?	+1	0	0	+1 [a]
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	+2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was readministered?	+2	−1	0	0
5. Are there alternative causes that could, on their own, have caused the reaction?	−1	+2	0	0
6. Did the reaction reappear when a placebo was given?	−1	+1	0	+1 [b]
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0 [c]
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
	Total Score: 6			

› Clin Pharmacol Ther. 1981 Aug;30(2):239-45. doi: 10.1038/clpt.1981.154.

A method for estimating the probability of adverse drug reactions

C A Naranjo, U Busto, E M Sellers, P Sandor, I Ruiz, E A Roberts, E Janecek, C Domecq, D J Greenblatt

PMID: 7249508 DOI: 10.1038/clpt.1981.154

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CASE REPORT | Open Access

Entecavir-induced neutropenia in an adult living donor liver transplant recipient: Successful conversion to tenofovir alafenamide

I. Vern Lim, Nurgül Özgür Yurttaş, Mesut Ayer, Şule Poturoğlu, Erdem Kınacı, İlgin Özden

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TEŞEKKÜRLER