# FMF-Konvansiyonel tedaviler ve aktivite kriterleri

**Dr. Gökhan Keser**

**E.Ü.T.F. İç Hastalıkları Romatoloji**

**V. Aydın Romatoloji Günleri**

**28.09.2019**

# Sunum Planı

- FMF Konvansiyonel Tedavisi
  - Kolşisine genel bakış
  - Kolşisine yetersiz yanıt
    - Tanımı?
    - Kolşisine yetersiz yanıt nedenleri?
- FMF Aktivite kriterleri

**Table 1** EULAR recommendations for the management of FMF with the level of agreement, of evidence and grade of recommendatio

| Recommendation | A |
|---|---|
| 01. Ideally, FMF should be diagnosed and initially treated by a physician with experience in FMF | 7.( |
| 02. The ultimate goal of treatment in FMF is to reach complete control of unprovoked attacks and minimising subclinical inflammation in between attacks | 9.3 |
| 03. Treatment with colchicine should start as soon as a clinical diagnosis is made | 8.5 |
| 04. Dosing can be in single or divided doses, depending on tolerance and compliance | 9.4 |
| 05. The persistence of attacks or of subclinical inflammation represents an indication to increase the colchicine dose | 9.1 |
| 06. Compliant patients not responding to the maximum tolerated dose of colchicine can be considered non-respondent or resistant; alternative biological treatments are indicated in these patients | 9.8 |
| 07. FMF treatment needs to be intensified in AA amyloidosis using the maximal tolerated dose of colchicine and supplemented with biologics as required | 9.5 |
| 08. Periods of physical or emotional stress can trigger FMF attacks, and it may be appropriate to increase the dose of colchicine temporarily | 7.( |
| 09. Response, toxicity and compliance should be monitored every 6 months | 8.( |
| 10. Liver enzymes should be monitored regularly in patients with FMF treated with colchicine; if liver enzymes are elevated greater than twofold the upper limit of normal, colchicine should be reduced and the cause further investigated | 8.4 |
| 11. In patients with decreased renal function, the risk of toxicity is very high, and therefore signs of colchicine toxicity, as well as CPK, should be carefully monitored and colchicine dose reduced accordingly | 9.3 |
| 12. Colchicine toxicity is a serious complication and should be adequately suspected and prevented | 9.4 |
| 13. When suspecting an attack, always consider other possible causes. During the attacks, continue the usual dose of colchicine and use NSAID | 9.5 |
| 14. Colchicine should not be discontinued during conception, pregnancy or lactation; current evidence does not justify amniocentesis | 9.3 |
| 15. In general, men do not need to stop colchicine prior to conception; in the rare case of azoospermia or oligospermia proven to be related to colchicine, temporary dose reduction or discontinuation may be needed | 8.2 |
| 16. Chronic arthritis in a patient with FMF might need additional medications, such as DMARDs, intra-articular steroid injections or biologics | 9.5 |
| 17. In protracted febrile myalgia, glucocorticoids lead to the resolution of symptoms; NSAID and IL-1-blockade might also be a treatment option; NSAIDs are suggested for the treatment of exertional leg pain | 9.3 |
| 18. If a patient is stable with no attacks for more than 5 years and no elevated APR, dose reduction could be considered after expert consultation and with continued monitoring | 8.( |

A, agreement (/10); APR, acute phase reactants; CPK, creatinine phosphokinase; DMARDs, disease modifying antirheumatic drugs; EULAR, European League Against Rheum
familial Mediterranean fever; IL-1, interleukin 1; LoE, level of evidence; NSAID, non steroidal anti inflammatory drugs.

# Ailevi Akdeniz Ateşi

- Kolşisin
  - 1972

    Prof. Dr. Emir Özkan

    Dr. S. E. Goldfinger


- Goldfinger SE. Colchicine for familial Mediterranean fever. N Engl J Med 1972; 287: 1302.
- Ozkan E, Okur O, Ekmekci A, Ozcan R, Tag T. A new approach to the treatment of periodic fever. Med Bull Istanbul 1972; 5: 44-9.

# FMF Tedavisinde Kolşisin

- FMF ataklarını ve amiloidoz gelişimini önlemek için kolşisin sürekli kullanılmalıdır. Gebelik ve laktasyonda kesilmemelidir. Atakları tam önlemese bile amiloidoz gelişimini engelleyebilir.
- Önerilen maksimum doz 2 mg/gün;
- Düşük dozda başla; bölünmüş dozda tok ver
- Tam remisyon: %65
- Parsiyel remisyon: %20–30
- Yanıtsız: %5–10

(Ben-Chetrit E, Levy M. Familial Mediterranean fever. Lancet1998;351:659–64).

# Kolşisin tedavisinde hasta uyumunu ve başarıyı etkileyen püf noktaları


Form: Draje

**Etkin madde: 0,5 mg kolşisin**

**Yardımcı maddelerin listesi**

Her bir çekirdek draje;

- Laktoz
- Mısır nişastası
- Primojel
- Ponceau 4R
- Talk
- Mg-stearat

Seker kaplama tabakası

- Şeker
- Arap zamkı
- Talk
- Titandioksit
- Ponceau 4R
- Ewaks


Form: Film tablet

**Etkin madde: 0,5 mg kolşisin**

**Yardımcı Maddelerin Listesi**

- Laktoz Monohidrat
- Mısır nişastası
- Talk
- Kollidon VA 64
- Magnezyum stearat
- Stearik asit
- Opadry II Red 85F250030
- Polivinil alkol
- Polietilen glikol
- Talk
- FD&C Yellow #6 Alüminyum Lake


Form: Film tablet

**Etken madde: Kristalize kolşisin 1000 mg**

**Yardımcı Maddelerin Listesi**

- Sakaroz
- Magnezyum sitrat
- Polyvidone (E 1201)
- Eritrosin gıda renklendirici (E127)
- Mikrokristalize selüloz

- Kolşisinin terapötik indeksi oldukça dar
  - Düzenli olarak günde 1.5-2 mg dozunda alındığında serum düzeyi genellikle <7 ng/ml
  - Toksik etkiler serum düzeyi >10 ng/ml olduğunda görülüyor
    - Gastrointestinal istenmeyen etkiler (bulantı, karın ağrısı ve ishal) toksik dozda ilaç almayı etkiliyor
      - Karaciğer ve böbrek yetersizliği
      - İlaç etkileşimleri

        Özellikle makrolid antibiyotikler ve siklosporin
      - İV yolla kolşisin kullanılması

*Semin Arthritis Rheum*. 2015 December ; 45(3): 341–350. doi:10.1016/j.semarthrit.2015.06.013.

# Colchicine --- update on mechanisms of action and therapeutic uses

**Ying Ying Leung**[1,2], **Laura Li Yao Hui**[1], and **Virginia B Kraus**[3]

RHEUMATOLOGY

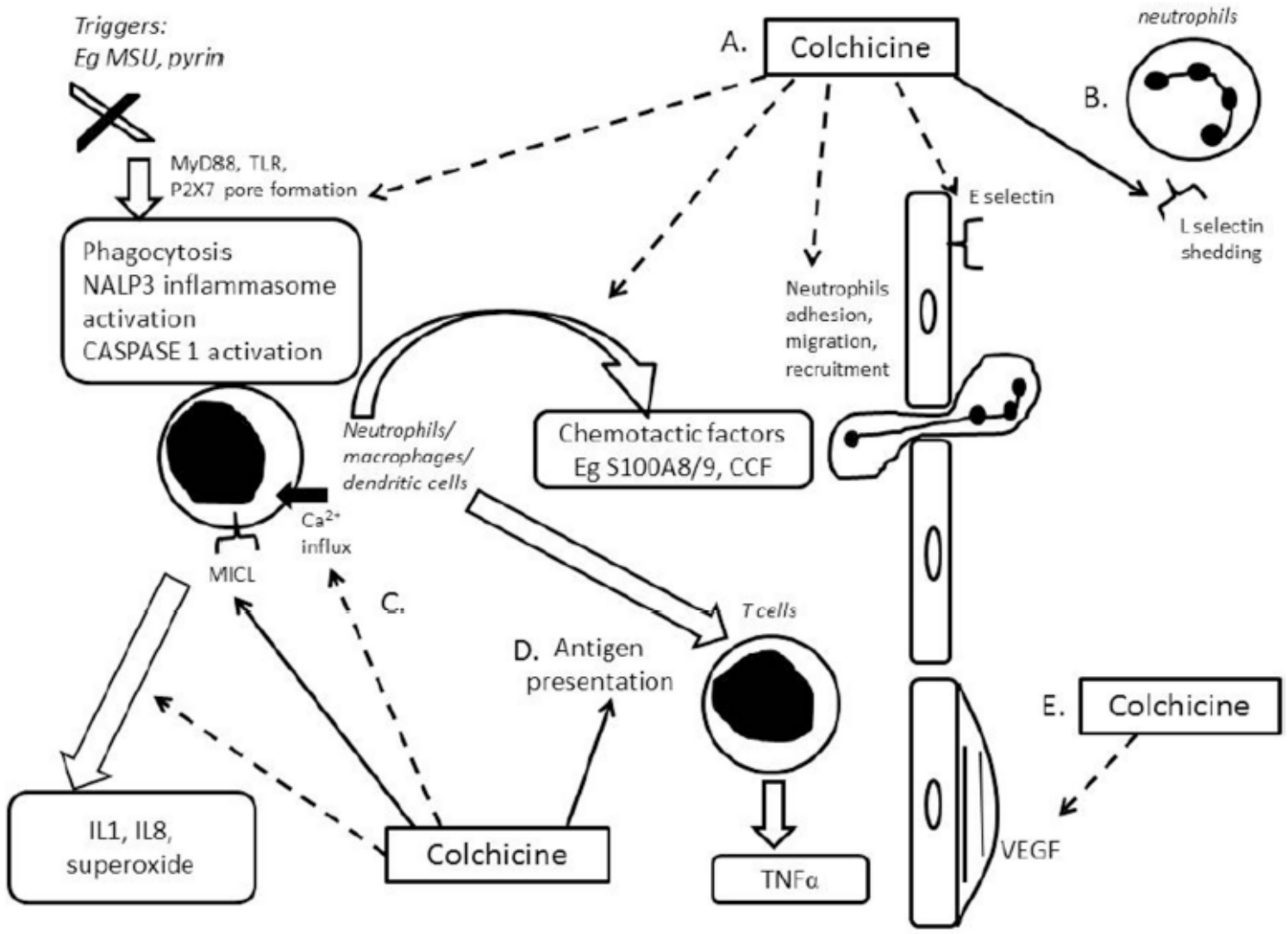
Rheumatology 2018;57:i4–i11
doi:10.1093/rheumatology/kex453

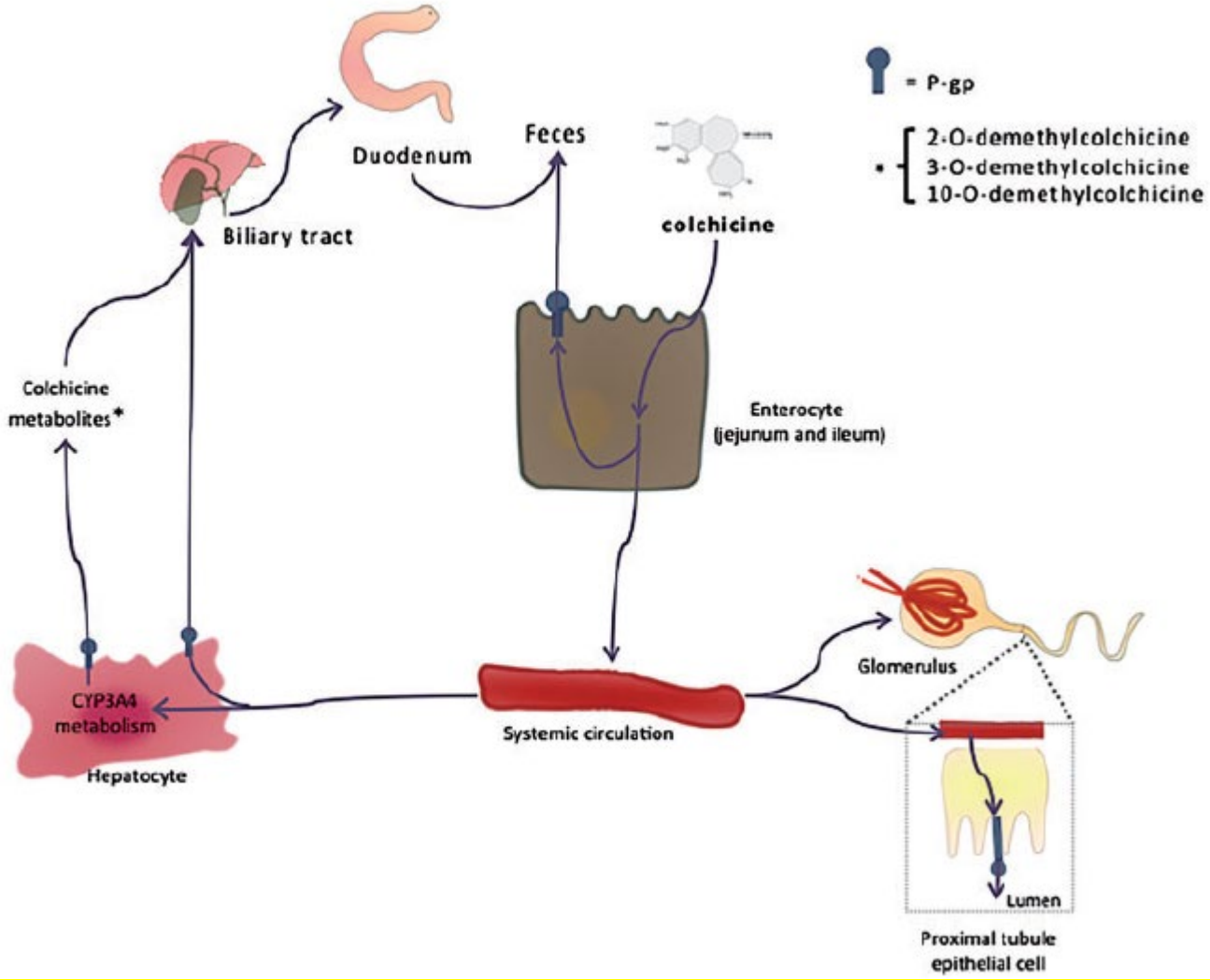
# Update on colchicine, 2017

**Anastasia Slobodnick**[1,2], **Binita Shah**[2,3], **Svetlana Krasnokutsky**[1,2] and **Michael H. Pillinger**[1,2]

**Serbest tubulin dimerlerine bağlanarak, tubulin polimerizasyonunu engelleyerek mikrotubul polimerizasyonu ve yapısını bozar. İnhibe ettiği pürinerjik reseptörler «pore» oluşumunda ve NALP3 inflamazom aktivasyonunda önemli……**








**P-glikoprotein** (P-gp); Diğer isimleri multidrug resistance protein 1 (**MDR1**) or ATP-binding cassette subfamily B member 1 (**ABCB1**) Hepatositlerde, proksimal renal tüp hc.lerinde, enterik hc.lerde, monositlerde , kan beyin bariyer hc.lerinde sunulur.

# Association of Drug Transporter Gene *ABCB1 (MDR1)* 3435C to T Polymorphism with Colchicine Response in Familial Mediterranean Fever

ABDURRAHMAN TUFAN, MELIH O. BABAOGLU, ALI AKDOGAN, UMIT YASAR, MERAL CALGUNERI, UMUT KALYONCU, OMER KARADAG, MUTLU HAYRAN, A. IHSAN ERTENLI, ATILA BOZKURT, and SEDAT KIRAZ

*ABSTRACT.* ***Objective.*** Colchicine is a mainstay of treatment in familial Mediterranean fever (FMF); however, 5%–10% of patients do not respond to colchicine. Adenosine triphosphate-binding cassette subfamily B member 1 (ABCB1 or MDR1) is a drug transporter that extrudes colchicine out of cells. *ABCB1* gene 3435C to T polymorphism has been demonstrated to alter MDR1 expression in mononuclear cells. Thus, the amount of MDR1 in mononuclear cells may alter response to colchicine. We investigated the association between *MDR1* 3435C to T polymorphism and colchicine response in patients with FMF.

***Methods.*** Patients (n = 120) were examined for colchicine responses. *ABCB1* gene 3435C to T genotypes were determined to analyze associations with colchicine resistance.

***Results.*** Ninety-eight patients were evaluated as responders and 22 as nonresponders. The distributions of *ABCB1* CC, CT, and TT genotypes were significantly different between responsive and nonresponsive groups (chi-square = 6.86, p = 0.032). Colchicine resistance was significantly higher in patients harboring the C allele than in patients with TT genotype (odds ratio 9.71, 95% CI 1.58–58.76). Similarly, the mean colchicine dose to prevent remission was significantly lower in the TT group compared with subjects with the C allele (p = 0.014).

***Conclusion.*** Our study revealed an association between 3435C to T polymorphism and colchicine response in patients with FMF. Patients with the TT genotype for the *ABCB1* 3435C to T variant responded better to colchicine in terms of treatment efficacy and colchicine dose requirements. (First Release June 15 2007; J Rheumatol 2007;34:1540–4)

*Renal Failure*, 33(9): 899–903, (2011)

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DOI: 10.3109/0886022X.2011.605980

informa
healthcare

LABORATORY STUDY

# Association between ABCB1 (*MDR1*) Gene 3435 C>T Polymorphism and Colchicine Unresponsiveness of FMF Patients

Filiz Ozen[1], Coskun Silan[2], Ahmet Uludag[3], Ferhan Candan[4], Fatma Silan[3], Semra Ozdemir[5], Sinem Atik[3] and Ozturk Ozdemir[1,3]

*[1]Department of Medical Genetics, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey; [2]Department of Pharmacology, Faculty of Medicine, Canakkale Onsekiz Mart University, Canakkale, Turkey; [3]Department of Medical Genetics, Faculty of Medicine, Canakkale Onsekiz Mart University, Canakkale, Turkey; [4]Department of Internal Medicine, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey; [5]Department of Nuclear Medicine, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey*

## Abstract

The multidrug resistance gene-1 (MDR1, adenosine triphosphate-binding cassette transporter: ABCB1, P-glycoprotein) encodes membrane proteins that play a crucial role in protecting cells from xenobiotics, chemicals, and drugs. The TT genotype of 3435 codon in exon 26 of *MDR1* gene causes overexpression of gene activity and effluxes many chemically diverse compounds across the plasma membrane. We studied the association between C3435T polymorphisms (single nucleotide polymorphism) of *MDR1* gene and colchicine-resistant familial Mediterranean fever (FMF) patients. Total genomic DNA samples from 52 FMF patients of colchicine unresponsiveness were used for FMF (*MEFV*) and *MDR1* genes profile analyses. Target genes were genotyped by multiplex PCR-based reverse-hybridization Strip Assay method. The preliminary current results showed increased T allele frequency (0.596) in colchicine unresponsiveness of FMF patients. The distributions of the CC, CT, and TT genotypes in colchicine nonresponder FMF patients were 17%, 46%, and 37%, respectively. Our results indicate that C3435T polymorphism in exon 26 of *MDR1* gene is associated with colchicine resistance in nonresponder FMF patients during the common therapy protocol.

| Strong CYP3A4 inhibitors | Moderate CYP3A4 inhibitors | P-glyco protein inhibitors |
|---|---|---|
| Clarithromycin | Cimetidine | Amiodarone |
| Cobicistat | Ciprofloxacin | Carvedilol |
| Diltiazem | Cyclosporine | Clarithromycin |
| Itraconazole | Erythromycin | Itraconazole |
| Ketoconazole | Fluconazole | Quinidine |
| Ritonavir | Fluvoxamine | Ranolazine |
| Telithromycin | Imatinib | Ritonavir |
| Voriconazole | Verapamil | Verapamil |

Greyfurt suyu !!

# «Kolşisin Tedavisine Yetersiz Yanıt» Kavramı

- Hastada gerçekten bu durum var mı?
- Yanıt evet ise, bu durumun nedenleri ne olabilir?
- Kolşisine yetersiz yanıtlı FMF'in tanımı nedir?
  - Maksimum doz ve tam kompliyans koşuluyla hangi hastaları, hangi koşullarda kolşisin tedavisine yetersiz yanıtlı kabul edelim?
  - Standart bir tanım !!!!

# "Kolşisin tedavisine yanıtsızlık var" demeden önce;

- Hasta ilacını yeterli dozda, düzenli ve uygun şekilde kullanıyor mu?
  - Max ilaç dozu ne kadar olmalı?
  - Önerilen max doz: 2 mg/gün
- Kompliyans tamsa FMF tanısı doğru mu ? (Ayırıcı tanıdaki hastalıklar gözden geçirilmeli)
- Preparat farkı (etkisi düşük ilaç) söz konusu olabilir mi?

# İki Sorunun Yanıtı Önemli:

- Kolşisine tedavisine yetersiz yanıtın tanımı nedir? Bunun nedenleri ne olabilir?

# «Yetersiz Yanıt» için herkes tarafından kabul edilmiş belli bir tanım yok.

Tolere edilebilen max kolşisin dozu ve tam kompliyans;

- Son 3 ayda, ≥1 atak/ay **(Gul A, et al. Arthritis Rheum. 2013)**
- >1 atak / 3 ay **(Ben-Chetrit E et al. Semin Arthritis Rheum 1991)**
- ≥1 atak/ay veya ataklar arasında ↑ AFR (≥1.5 kat CRP, ESH, SAA) **(NIAMS: Clinicaltrials.gov., NCT00094900)**
- Yılda 6 kez tipik atak geçirmesi veya 4-6 ayda bir 3'den fazla tipik atak geçirmesi ve atipik ataklarda 3 akut faz reaktanından (CRP, ESR, SAA) en az ikisinin ataklar arasında yüksek seyretmesi
  **(Hentgen V et al, Semin Arth Rheum, 2013)**

# Which definition should be used to determine colchicine resistance among patients with familial Mediterranean fever?

A. Erden[1], E.D. Batu[2], A. Sarı[1], H.E. Sönmez[2], B. Armagan[1], S. Demir[2], E. Fırat[3], Y. Bilginer[2], S.A. Bilgen[1], O. Karadag[1], U. Kalyoncu[1], S. Kiraz[1], I. Ertenli[1], S. Ozen[2], A. Akdogan[1]

- *Anti-IL-1 tedavi alan 40 erişkin, 20 çocuk hasta*
- *Toplam 12 farklı tanım sınanıyor*
- *%93.3 olgu tanım 5'i karşılamış (en yüksek)*
- *%26 olgu tanım 9'u karşılamış (en düşük)*
- *Tanım 4 & 6'yı karşılayan hasta oranı erişkinlerde anlamlı yüksek*
- *Klinik atak olmayan hastalar dışlandığında, en yüksek uyum tanım 2'de (%94.4)*

**Erden A, et al. *Clin Exp Rheumatol 2018; 36 (Suppl. 115): S00-S00.***

| | |
|---|---|
| Definition 1 (16) | Despite taking adequate colchicine treatment, at least 1 episode per month (≥6 years, ≥1.5 mg/day for at least 3 months or <6 years, ≥1.2 mg/day) |
| Definition 2 (4, 11, 17) | Despite taking ≥2 mg/day* colchicine, more than 1 typical episode per 3 months |
| Definition 3 (10) | Despite ≥receiving 2 mg/day* colchicine, 3 or more attacks within the last 6 months |
| Definition 4 (18) | i) Despite the fact that adequate doses of colchicine (maximum dose of colchicine is 2 mg/day for adolescents and for younger children as the maximum tolerated dose), at least one episode per month during the following 3 months and increased ESR or increased CRP or increased SAA between attacks<br>ii) Presence of amyloidosis<br>iii) Protracted febrile myalgia and frequent need of steroid treatment<br>iiii) Presence of persistent arthritis |
| Definition 5 (8) | i) More than 3 episodes in 4-6 months, or more than 6 typical episodes per year, despite full compliance to treatment<br>ii) In case of incomplete attacks, an increase in at least two out of three APRs (CRP, ESR, and SAA) between attacks |

Erden A, et al. *Clin Exp Rheumatol 2018; 36 (Suppl. 115): S00-S00.*

| | |
|---|---|
| Definition 6 (19) | i) One or more episodes per month despite the use of maximum tolerated dose of colchicine for at least 6 months<br>ii) and/or presence of amyloidosis |
| Definition 7 (12) | i) At least 1 episode per month despite taking 2 mg/day* colchicine<br>ii) Persistently elevated APR<br>iii) Organ involvement (especially renal)<br>iiii) Losing job or not continuing to school |
| Definition 8 (6) *(NIAMS:Clinicaltrials.gov., NCT00094900, Interleukin-1 trap in the treatment of autoinflammatory diseases)* | i) Despite taking ≥2 mg/day* of colchicine, at least 1 episode per month<br>ii) Symptoms continue despite ≥2 mg/day* colchicine intake<br>iii) ESR, CRP or SAA elevation ≥1.5 times higher than the normal limit between attacks despite treatment with maximally tolerated dose of colchicine. |
| Definition 9 (9) | Despite 2 mg* of colchicine, at least 2 episodes per month and elevation of CRP and SAA between attacks |
| Definition 10 (7, 20) | In presence of at least two *MEFV* mutations, and at least one attack per month in any of the FMF sites despite maximum tolerated dose of colchicine |
| Definition 11 (21) | ≥3 episodes during 3 months despite treatment with colchicine at ≥1-2 mg/day (based on age) for at least 3 months |

**Erden A, et al. *Clin Exp Rheumatol 2018; 36 (Suppl. 115): S00-S00.***

- *%93.3 olgu tanım 5'i karşılamış (en yüksek)*
- *%26 olgu tanım 9'u karşılamış (en düşük)*
- *Tanım 4 & 6'yı karşılayan hasta oranı erişkinlerde anlamlı ↑*
- *Klinik ataksız hastalar dışlandığında, en yüksek uyum tanım 2'de (%94.4)*
- *Tanım 2'deki atak sıklığı (>1 tipik atak /3 ay) + Tanım 5'deki amiloidoz varlığı/ AFY yüksekliği (≥2/3 AFY yüksekliği)*
- ***Maks. tolere kolşisin dozunu almasına rağmen; üç ay içinde birden fazla atak, VEYA ataksız dönemde* CRP, ESH, SAA üçlüsünün en az ikisinde artış , VEYA amiloidoz varlığı**

**Erden A, et al. *Clin Exp Rheumatol 2018; 36 (Suppl. 115): S00-S00.***

# Tedavi yanıtsızlığı netleştikten sonra

- Hangi atak bulguları tedavi ile önlenemiyor veya düzeltilemiyor?
  - Tipik AAA atakları?
  - Uzamış artrit atakları?
  - Uzamış febril miyalji?
- Kolşisin tedavisine yanıtsızlıktan

AAA'ne eşlik edebilen HSP, PAN gibi vaskülitler veya SpA gibi romatizmal hastalıklar sorumlu olabilir mi?

Best Practice & Research Clinical Rheumatology 30 (2016) 296–303

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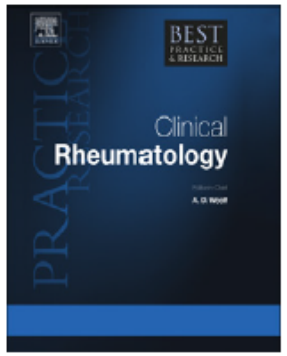


6

# Approach to the patients with inadequate response to colchicine in familial Mediterranean fever

Ahmet Gül

%5

# Kolşisine Yanıtsızlık Nedenleri

***Genetik faktörler***

- Kolşisinin GI emiliminin yetersiz olması
  - % 24-88 arasında değişebilir
- Lökosit içi konsantrasyon yetersizliği
  - Kan hücreleri veya serozal membran hücrelerinde MDR1 geni fonksiyonu ile ilgili sorunlarSNP'ler
    - Tufan A et al., J Rheumatol. 2007, 34(7): 1540-44
    - Ozen F et al., Renal Fail. 2011, 33(9): 899-903
- M694V homozigot mutasyonu
- SAA polimorfizmleri

# Kolşisine Yanıtsızlık Nedenleri

## *Çevresel faktörler*

- Mikrobiyota (WT ve mutant allellerin etkisi)
- Enfeksiyonlar
- Aşırı fiziksel aktivite
- Soğuğa maruziyet
- Emosyonel stres, diyet, menstruasyon
- İlaç etkileşmeleri
  - Kolşisin metab. ile ilgili sorunlar (CYP3A4 düzeyinde)
- Sosyoekonomik düzey
- Eşlik eden diğer hastalıklar
- Düşük D vitamini düzeyi

**Table 2**
Factors affecting the response to colchicine in familial Mediterranean fever [10].

| |
|---|
| **A. Factors associated with higher inflammatory activity or severe disease course in FMF** |
| a. Homozygosity for p.Met694Val variant in exon 10 of the MEFV gene |
| b. Other genetic factors aggregating within families and increasing the inflammatory burden |
| c. Environmental factors |
| d. Accompanying inflammatory conditions (e.g., spondyloarthritis and systemic vasculitis) |
| **B. Factors associated with colchicine bioavailability** |
| a. Compliance |
| b. Absorption, metabolism, and intracellular concentration |
| i. Genetic polymorphisms affecting the transport and metabolism of colchicine |
| c. Drug interactions |
| i. Drugs interacting with CYP3A4 and ABCB1 proteins |
| d. Intolerance |
| i. Individual factors affecting the gastrointestinal tolerance to colchicine treatment |

# Kolşisine alternatif diğer tedaviler

- Talidomid: Etkinlik bildirilmiş, yan etkisi fazla
- Interferon alfa: Çelişkili sonuçlar
- SSRI: Az sayıda hastada
- Dapson: Olgu sunumu
- AZA: FMF, amiloidoz, nefropati olgusunda
- Biyolojikler
  - **Anti-IL-1 ajanlar**
  - TNFi ajanlar; olgu bildirimleri (FMF, FMF+AS)


- Gül A. Best Practice & Research Clinical Rheumatology, 2016.
- Salehzadeh F, et al. Case Reports in Rheumatology, 2019.
- Özçakar L, et al. Rheumatol Int, 2005.
- Sayarlıoğlu H, et al. Rheumatol Int, 2006.
- Seyahi E, et al. *Clin Exp Rheumatol, 2002.*

# FMF Aktivitesinin Değerlendirilmesi

*Ann Rheum Dis.* 2011 February ; 70(2): 309–314. doi:10.1136/ard.2010.132613.

## A preliminary score for the assessment of disease activity in hereditary recurrent fevers: results from the AIDAI (Auto-Inflammatory Diseases Activity Index) Consensus Conference

**Maryam Piram[1], Joost Frenkel[2], Marco Gattorno[3], Seza Ozen[4], Helen J Lachmann[5], Raphaela Goldbach-Mansky[6], Véronique Hentgen[7], Bénédicte Neven[8], Katia Stankovic Stojanovic[9], Anna Simon[10], Jasmin Kuemmerle-Deschner[11], Hal Hoffman[12], Silvia Stojanov[13], Agnès Duquesne[14], Pascal Pillet[15], Alberto Martini[3], Jacques Pouchot[16], and Isabelle Koné-Paut[1] on behalf of the EUROFEVER and EUROTRAPS networks**

## Validation of the Auto-Inflammatory Diseases Activity Index (AIDAI) for hereditary recurrent fever syndromes

**Piram M, et al. Ann Rheum Dis 2014;73:2168–2173.**

Maryam Piram,[1] Isabelle Koné-Paut,[1] Helen J Lachmann,[2] Joost Frenkel,[3] Seza Ozen,[4] Jasmin Kuemmerle-Deschner,[5] Silvia Stojanov,[6] Anna Simon,[7] Martina Finetti,[8] Maria Pia Sormani,[9] Alberto Martini,[8,10] Marco Gattorno,[8] Nicolino Ruperto,[8] on the behalf of EUROFEVER, EUROTRAPS and the Paediatric Rheumatology International Trials Organisation (PRINTO) networks

# FMF ve diğer otoinflamatuvar patolojilerde hastalık aktivitesi tayini için seçilen parametreler

Variables selected during consensus conference to assess disease activity

| FMF | MKD | TRAPS | CAPS |
|---|---|---|---|
| Fever ≥38°C (100.4°F) | Fever ≥38°C (100.4°F) | Fever ≥38°C (100.4°F) | Fever ≥38°C (100.4°F) |
| Abdominal pain | Abdominal pain | Abdominal pain | Limb pain |
| Arthralgia or myalgia | Nausea/vomiting | Limb pain | Conjunctivitis |
| Swelling of the joints | Diarrhoea | Eye manifestations | Headaches |
| Chest pain | Limb pain | Skin rash | Skin rash |
| Skin rash | Painful lymph nodes | Overall TRAPS symptoms | |

CAPS, cryopyrin-associated periodic syndromes; FMF, familial Mediterranean fever; MKD, mevalonate kinase deficiency;TRAPS, TNF receptor-1-associated periodic syndrome.

**Table 3**

Diary for patients with familial Mediterranean fever (FMF)

| FMF-related symptoms today | | | | | | | |
|---|---|---|---|---|---|---|---|
| Name: | | | Month: | | | | Year: |
| Days | Fever ≥38°C (100.4°F) | Abdominal pain | Chest pain | Arthralgia or myalgia | Swelling of the joints | Skin rash | Pain relief taken |
| Scored as: | 0 or 1 | 0–3 | 0–3 | 0–3 | 0–3 | 0–3 | 0 or 1 |
| 1 | | | | | | | |
| 2 | | | | | | | |
| … | | | | | | | |
| 31 | | | | | | | |
| Total | (a) | (b) | (c) | (d) | (e) | (f) | Total (a+b+c+d+e+f) |

Netherlands The Journal of Medicine 2007, 65(9): 318-24.

REVIEW

# Familial Mediterranean fever: clinical, molecular and management advancements

M. Lidar*, A. Livneh

**Table 1.** *Familial Mediterranean fever disease severity score*

| Subgroup | Severity | Number of features | Features |
|---|---|---|---|
| Patients either not yet taking colchicine or not responding to colchicine therapy | Severe | 2 or more | 1. ≥2 attacks per month<br>2. Involvement of more than 1 attack site in >25% of attacks<br>3. Involvement of more than 2 attack sites during the disease course |
| | Moderate | 1 or more | 1. 18-24 attacks/year<br>2. Attack duration ≥4 days, on most attacks |
| | Mild | | Neither severe nor moderate disease |
| Patients under optimal colchicine therapy* | Severe | 3 or more | 1. Involvement of more than 1 attack site in >25% of attacks<br>2. Involvement of more than 2 attack sites during the disease course<br>3. ≥2 mg/d colchicine (or less if intolerant)<br>4. ≥2 pleuritic attacks during disease course<br>5. ≥2 erysipeloid-erythema attacks during disease course<br>6. Age of onset ≤10 years |
| | Moderate | 2 | |
| | Mild | 0-1 | |

*Attack-related features (e.g. frequency, site affected, etc.) refer to disease activity prior to colchicine treatment.

EXTENDED REPORT

# FMF50: a score for assessing outcome in familial Mediterranean fever

Seza Ozen,[1] Erkan Demirkaya,[2] Ali Duzova,[1] Ozlem Erdogan,[3] Eren Erken,[4] Ahmet Gul,[5] Ozgur Kasapcopur,[6] Timucin Kasifoglu,[7] Bunyamin Kisacik,[8] Huri Ozdogan,[5] Mehmet Tunca,[9] Cengizhan Acikel,[10] for the FMF Arthritis Vasculitis and Orphan disease Research in pediatric rheumatology (FAVOR) and Turkish FMF study group

**Ann Rheum Dis 2014;73:897–901.**

# FMF50 Yanıtı: Aşağıdaki 6 parametrenin en az 5'inde %50 düzelme olurken, kalan kriterde kötüleşme yok

- Tedavi ile atak sıklığında değişiklik yüzdesi
- Tedavi ile atak süresinde değişiklik yüzdesi
- Hastanın/anne ve babanın hastalık şiddeti global değerlendirmesi (10 cm VAS)
- Doktorun hastalık şiddeti global değerlendirmesi (10 cm VAS)
- Tedavi ile artrit atak değişiklik yüzdesi
- Tedavi ile CRP, ESH veya SAA düzey değişiklik yüzdesi (son ataktan en az 2 hafta sonra)

**Ozen S, Demirkaya E, Duzova A, et al. Ann Rheum Dis 2014;73:897–901.**

**İLGİNİZ İÇİN**

**TEŞEKKÜRLER**