



# BEHÇET HASTALIĞI MUKOKUTANÖZ BELİRTİLER VE TEDAVİSİ

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# Behçet Hastalığı (BH)

## ■ Tanım:

1. ROÜ
2. GÜ
3. Üveit
4. Sistemik: Artiküler, vasküler, GI, nörolojik ve kardiyo-pulmoner vb.





# Epidemiyoloji:

- Genç bireyler, 20–40 yaş, en sık etkilenir
- E/K oranı genellikle 1 : 1
- İpek yolu boyunca yerleşen ülkelerde en sık prevalans (1/10,000 and 1/1,000)

# Clinical features and natural course of Behçet's disease in 661 cases: a multicentre study

E. Alpsoy, L. Donmez,\* M. Onder,† S. Gunasti,‡ A. Usta,§ Y. Karıncaoglu,¶ B. Kandi,\*\* S. Buyukkara, O. Keseroglu,† S. Uzun,‡ U. Tursen,§ M. Seyhan¶ and A. Akman British Journal of Dermatology 2007

*Conclusions* Mucocutaneous lesions are the hallmarks of the disease, and especially oral ulcers precede other manifestations. The increase in clinical severity score is more pronounced in patients without regular treatment and follow-up. Male sex and a younger age at onset are associated with more severe disease.

# Prognoz:

- Göz ve SSS tutulumu en temel prognostik faktörler
- KVS, AC ve GiS tutulumları en sık mortalite nedenleri

# Evaluation of clinical findings according to sex in 2313 Turkish patients with Behçet's disease

Umit Tursen, MD, Aysel Gurler, MD, and Ayse Boyvat, MD

*International Journal of Dermatology* 2003, **42**, 346–351

**Conclusions** Only genital aphthae and erythema nodosum were more frequent in females. On the other hand papulopustular eruptions, thrombophlebitis, ocular, neurologic, pulmonary and vascular involvement were more frequent in males. While female patients had the best prognosis, male patients had a worse overall prognosis than females.

# Etiyoloji:

- Genetik yatkınlık (HLA-B51)
- İnfeksiyonlar (Streptokokus)
- İmmunolojik disfonksiyonlar (Th1/17)

Türsen Ü. Pathophysiology of the Behçet's Disease. *Pathology Research International*. 2012;2012:493015. doi:10.1155/2012/493015

Association of class I HLA antigens with the clinical manifestations of Turkish patients with Behçet's disease

**T. I. Kaya, U. Tursen, A. Gurler\* and H. Durt**

HLA-B51 and the absence of HLA-B35 can be regarded as laboratory risk factors of venous thrombosis in patients with Behçet's disease.

2002 Blackwell Science Ltd • *Clinical and Experimental Dermatology*, **27**, 498–501

# **Genetic mutations and polymorphisms**

Umit Tursen · Tamer Irfan Kaya · Gulcin Eskandari  
Ozgur Gunduz · Müjde Yazar · Guliz Ikizoglu  
Ugur Atik

## **Association of factor V Leiden and prothrombin gene mutation with Behçet's disease**

Arch Dermatol Res (2001) 293 : 537–539

## **Association of the platelet glycoprotein Ia C807T/G873A gene polymorphism and thrombosis in Behçet patients**

GÜRBÜZ POLAT<sup>1,\*</sup>, GÜLÇİN ESKANDARI<sup>1</sup>, TAMER IRFAN KAYA<sup>2</sup>,  
ÜMIT TÜRSEN<sup>2</sup>, ÖZLEN BAGDATOĞLU<sup>1</sup>, GÜLİZ IKIZOĞLU<sup>2</sup>  
and UGUR ATIK<sup>1</sup> *Haematologia*, Vol. 32, No. 2, pp. 121–128 (2002)



Umit Tursen · Lulufer Tamer · Gulcin Eskandari  
Tamer Irfan Kaya · Nurcan Aras Ates · Guliz Ikizoglu  
Ugur Atik

## **Glutathione S-transferase polymorphisms in patients with Behçet's disease**

Arch Dermatol Res (2004) 296: 185–187

## N-acetyltransferase 2 polymorphisms in patients with Behcet's disease

L. Tamer, U. Tursen,\* G. Eskandari, N. A. Ates,† B. Ercan, H. Yildirim and U. Atik

2005 Blackwell Publishing Ltd • *Clinical and Experimental Dermatology*, 30, 56–60

## **Cytochrome P450 polymorphisms in patients with Behcet's disease**

Umit Tursen, MD, Lulufer Tamer, PhD, Hale Api, MD, Hatice Yildirim, PhD, Kiyemet Baz, MD, Guliz İkizoglu, MD, and Ugur Atik, PhD

*International Journal of Dermatology* 2007, 46, 153–156

# Klinik Bulgular

## Mukokutanöz lezyonlar



1. OÜ: Minör (%80), majör, herpetiform

2. GÜ: %80-90, skarlar tanısal, LAP, ağrı

3. EN-benzeri lezyonlar

4. PPE

5. Yüzeysel tromboflebit

6. Paterji testi

7. Diğer: Ekstragenital ülserler (İnguinal, aksilla, perianal, meme altı), Sweet send, piyoderma gangrenosum, LCV, EM-benzeri, pernio-benzeri, PAN-benzeri, gerçek arteriyel lezyonlar, subungual infarktlar



# Sistemik belirtiler

- Oküler: Anterior ve posterior üveit, retinal vaskülit
- Kas-iskelet: Artralji, artrit, osteonekroz, miyozit
- Vasküler: DVT, arteriyel oklüzyon ve anevrizma
- SSS: Santral motor parezi, beyin sapı ve serebellar belirtiler.
- GiS: En sık özefagus, terminal ileum, kolon ve rektumda ülserler.
- AC: Pulmoner arteriyel anevrizma, infarkt, hemoraji, plevral efüzyon, fokal veya diffüz fibrosis.
- Kalp: Valvuler lezyonlar, miyokardit, endomiyokardiyal fibrosis, perikarditis, intrakardiyak tromboz, koroner vaskülit ve ventriküler anevrizmalar.

## Clinical Manifestations of Behçet's Disease: An Analysis of 2147 Patients

Aysel Gürler, Ayşe Boyvat, and Ümit Türsen

*To evaluate the prevalence of the clinical findings in Behçet's disease, we retrospectively analyzed the clinical data of 2147 Behçet patients from 9 to 87 years of age (mean age 38.3 years) followed up during the years 1976 through 1997. One thousand ninety three patients were male and 1054 patients were female. The male/female ratio was 1.03. The mean age at onset was 25.6 years. A family history of Behçet's disease was present in 7.3 % of the patients. Positive pathergy was found in 1220 (56.8%) patients. All of the patients had mucocutaneous lesions. Out of the 2147 patients the disease manifested itself as only mucocutaneous involvement in 1168 patients. The prevalence of systemic manifestations was found as follows: 28.9% ocular involvement, 16.0% musculoskeletal involvement, 16.8% vascular involvement, 2.8% gastrointestinal involvement, 2.2% neurological involvement. Pulmonary involvement was seen in 20 (1.0%) patients, cardiac involvement was seen in 3 patients and renal involvement was observed in 2 patients. Male patients had vascular involvement 5.02, neurologic involvement 2.21 and ocular involvement 1.98 times more frequently than female patients.*

# Tanı

- Tamamen klinik tanı.
- BH Uluslararası çalışma grubu (ISG) yeni tanı kriterleri.
- ROÜ + en az 2 kriter;
- Göz tutulumu, GÜ, EN-benzeri lezyonlar ve PPE, paterji testi pozitifliği

Table 2 The older and newer criteria for the diagnosis of Behçet disease

## ISG criteria for the diagnosis of Behçet disease<sup>80</sup>

|                               |  |
|-------------------------------|--|
| Recurrent oral ulceration:    | Minor aphthous, major aphthous, or herpetiform ulcers observed by the physician or patient, which have recurred at least three times over a 12-month period            |
| Plus any 2 of the following:  |  |
| Recurrent genital ulceration: | Aphthous ulceration or scarring observed by the physician or patient   |
| Eye lesions:                  | Anterior uveitis, posterior uveitis, or cells in the vitreous on slit-lamp examination; or retinal vasculitis detected by an ophthalmologist                           |
| Skin lesions:                 | Erythema nodosum observed by the physician or patient, pseudofolliculitis, or papulopustular lesions; or acneiform nodules observed by the physician in postadolescent |
| Positive pathology test:      | Test interpreted as positive by the physician at 24-48 hr  |

These criteria are valid in the absence of other clinical explanation

## International criteria for Behçet disease point score system: scoring $\geq 4$ indicates Behçet diagnosis<sup>112</sup>

| Sign/symptom                         | Points         |
|--------------------------------------|----------------|
| Oral aphthosis                       | 2              |
| Genital aphthosis                    | 2              |
| Ocular lesions                       | 2              |
| Skin lesions                         | 1              |
| Neurologic manifestations            | 1              |
| Vascular manifestations              | 1              |
| Positive pathology test <sup>a</sup> | 1 <sup>a</sup> |

# TEDAVİ

- BH deęişik belirtilerinin tedavisi hala **tartışmalıdır.**
1. Durumun heterojenitesi
  2. Güvenli laboratuvar belirteçlerin eksikliği
  3. RKÇ eksikliği

# Kanıtı Dayalı Tıp Tedavisi

## ■ RKÇ

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*Global Journal of Dermatology & Venereology, 2014, 2, 27-49*

## Treatment Options in Behcet's Disease

Ümit Türsen<sup>1,\*</sup> and Belma Türsen<sup>2</sup>




# Kolşisin

- 1975' ten beri BH için kullanılıyor.
- İlk RKÇ 1980 yılında.
- 6 ay sonunda EN–benzeri lezyon ve artralji azalması.



- Diğer çift-kör bir çalışmada Cyc' den etkisiz.
- Son KÇ (2-yıl çift-kör);
- **GÜ, EN ve artritte kadınlarda, erkeklerde**  
**sadece artritte etkili.**



ments.<sup>6</sup> Therefore we believe that the low frequency of ocular and neurologic involvement in our patients may be result of the beneficial effect of the colchicine therapy we initiated at the time of diagnosis, early in the course of the disease. The

Report


**Evaluation of clinical findings according to sex in 2313 Turkish patients with Behçet's disease**

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*International Journal of Dermatology* 2003, **42**, 346–351

# Azatiyopirin:

- 2 mg/kg/gün göz tutulumunda 2 yıl boyunca etkili.
- OGÜ ve artrit belirtilerinde faydalı.
- DVT önleme kapasitesi var.

- 
- Entero- ve nöro-Behçet' te etkili.
  - Steroidden kurtarıcı ajan.
  - Erken dönem AZA başlanması uzun dönem prognozda faydalı.

# Siklosporin

- Retinal vaskülit gibi şiddetli göz tutulumlarında ilk tercih.
- Hem göz hem de MK lezyon ataklarını önler.
- Uzun dönemde SSS ve renal toksisite!!!

# Talidomid

- 24 haftalık çalışmada OGÜ ve PPE tedavisinde etkili.
- Rekürrens kesilince kaçınılmaz!!!
- Kolit? EN kötüleşmesi? !!!

- Nöro-BH, piyoderma gangrenozum, üveit ve GiS ülserlerinde de etkili.
- Özellikle doğurganlık çağında kadınlarda MK lezyonlar için ilk tercih olmamalı !!!
- Lenalidomid (anti-TNF- $\alpha$  ve anti-IL-6) dirençli kompleks aftosis te etkili.

# NSAİİ

- Azapropazon, 300 mg x3/gün, akut artritte etkisiz olup, ilk hafta için analjezi sağlar.
- Oral indometazin 25 mg x 4/ gün 3 ay kullanıldığında eklem şikayetlerinde faydalı.



# İnterferon

- IFN- $\alpha$ -2a, s.c., 6 MIU haftada 3 kez, **OGÜ ve PPE sayısını anlamlı azaltır.**
- Açık çalışmalarda, IFN- $\alpha$  (3-6 MIU) şiddetli arka üveitte etkili

- Kontrolsüz alıřmalara gre, IFN hem **okler** **hem de ekstraokler belirtileri** (nrolojik, artikler), azaltıp, uzun sreli remisyon saęlayabilir.
- Yksek maliyet ve sık YE (AZT ile birlikte miyelo-supresyon, depresyon veya psikoz) yaygın kullanımını kısıtlar.

# Anti-TNF ajanlar

- Etanersept RKÇ' ya göre MK-BH' ında etkili (OGÜ, PPE, artrit, Paterjiye etkisiz), olgu bildirilerinde göz tutulumu ??
- Diğer bir RKÇ' da ise MK-BH' ında etkisiz, bu olgular sonrasında IFX tedavisine yanıt verebilmiştir.

■ **İFX** geleneksel immunosupresiflere dirençli olgularda artrit, göz, GiS, nörolojik ve vasküler tutulumda kullanılması tavsiye edilen biyolojik ???

■ **Adalimumab**: Çoğu olgu bildirisi olmak üzere **göz tutulumu (FDA onaylı)**, **alt ekstremitte ülserleri**, **GÜ**, serebral vaskülit, GiS, **venöz tromboz da etkili.**

■ Golimumab diğer anti-TNF' lere dirençli hastalarda üveitte etkili ??

■ Yüksek maliyet ve YE' ler endişe kaynağı !!!

# Kortikosteroidler

- Depo KS (40 mg MP asetat her 3 haftada 1), Puls MP 1g/g 3 gün, sonra prednizon 1mg/kg/g) MK-BH için etkili
- Kadınlarda EN ataklarını önler.
- EULAR şiddetli sistemik BH ataklarının erken fazında kısa süreli kullanılmasını tavsiye eder.
- Topikal KS, OGÜ başlangıç fazı, dirençli lezyonlarda IL KS, ön üveitte optalmik KS damla önerilir

# Dapson

- 12-aylık RKÇ (100 mg/gün) MK-BH (OÜ, PPE, EN, Paterji) etkili.

Sharquie KE, Najim RA, Abu-Raghif AR. J Dermatol. 2002;29(5):267-79.

Convit J, Gohman-Yahr M, Rondón-Lugo AJ. Br J Dermatol. 1984;111(5):629-30

# Diğer İlaçlar

- Klorambusil (Göz, SSS)
- Siklofosfamid (Vasküler=VCSS, Budd-Chiari send, nörolojik, gözde KE-EULAR)
- Metotreksat (Göz, SSS, MK-BH)
- Antibiyotik (Benzatin penisilin, minosiklin, azitromisin, eritromisin)
- Pentoksifilin (Göz, iskemik bacak ülserleri)
- Levamizol (OGÜ, artrit, ve üveit)
- Takrolimus (Oküler, GI BH)
- Mikofenolat mofetil (MK-BH ve nörolojik)

- GM-CSF (GÜ)
- Granülosit ve monosit adsorpsiyon aferezi (Ağrılı OGÜ ve oküler-BH)
- İVİG (Oküler-BH)
- Oral laktobasil ve düşük doz doğal insan IFN' u- içeren pastiller (OÜ)
- Pimekrolimus krem (GÜ, ağrı giderici)

[Pimecrolimus versus placebo in genital aphthous ulcers of Behçet's disease: a randomized double-blind controlled trial.](#)

Chams-Davatchi C, Barikbin B, Shahram F, Nadji A, Moghaddassi M, Yousefi M, Davatchi F.

Int J Rheum Dis. 2010;13(3):253-8.

[Randomized trial of pimecrolimus cream plus colchicine tablets versus colchicine tablets in the treatment of genital ulcers in Behçet's disease.](#)

Köse O, Dinç A, Simşek I. Dermatology. 2009;218(2):140-5.



- Antikoagölasyon ted: DVT, SVO, arteriyel?
- Rebamipid, benzidamin hidroklorid gargara, Amlexanox 5% oral macun, topikal PG-E2 jel, klorhekzidin jel, triklosan, tetrasiklin ve minosiklin gargara, NdYag lazer, topikal anestetikler, anti-mikrobiyal gargaralar, çinko sülfat (OÜ)

- Sükralfat: OGÜ

- Cerrahi (GI, Vasküler)



# Severe erythema nodosum due to Behçet's disease responsive to erythromycin

T Irfan Kaya<sup>1</sup>, U Tursen<sup>1</sup>,  
K Baz<sup>1</sup>, G Ikizoglu<sup>1</sup> and  
D Dusmez<sup>2</sup>

Departments of <sup>1</sup>Dermatology and  
<sup>2</sup>Pathology, Faculty of Medicine, Mersin  
University, Mersin, Turkey

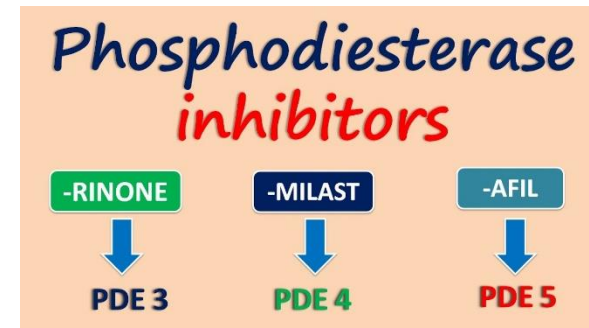
**A patient with severe erythema nodosum due to Behçet's disease is reported on here. Erythema nodosum lesions did not respond to classical treatments; however, they cleared after erythromycin treatment, which was prescribed for the treatment of coincidental erythrasma. Erythromycin treatment**

**appears to be an effective treatment option in erythema nodosum. The hypothetical anti-inflammatory effects of erythromycin, besides its antibiotic properties, are reviewed and discussed to explain such a clinical improvement. (J Dermatol Treat (2003) 14: 1–4)**

- [N Engl J Med.](#) 2015 Apr 16;372(16):1510-8.
- **Apremilast** (30 mg/günde 2 kez 12 haftalık); **RKÇ OÜ'** de etkili.

[Hatemi G, Melikoglu M, Tunc R, Korkmaz C, Turgut Ozturk B, Mat C, Merkel PA, Calamia KT, Liu Z, Pineda L, Stevens RM, Yazici H, Yazici Y.](#)

**FDA Onayı: Apremilast  
(*Otezla*) BH OÜ !!!!  
Temmuz 22, 2019**



# Diğer biyolojikler

- Rituksimab: Göz
- Gevokizumab (Göz), Canakinumab (anti-IL-1 $\beta$ ):  
Göz, GIS, OGÜ, SSS, vasküler
- Anakinra: OGÜ + GI + artiküler-BH
- Tokilizumab (anti-IL6, reküren meningo-ensefalit ve üveit)

# Tedavi Sonu:

- Üveit, OGÜ ve artritte genel olarak kanıta dayalı tedavi var.
- Diğer organ tutulumu tedavisi (damar, SSS ve GİS) ise genel olarak uzman yorumuna dayalı.

| Manifestations   | Treatments  |
|--|---|
| Oral apthae  | 1 <sup>st</sup> line: Topical triamcinolone acetonide, prednisolone, amlexonax, anti-inflammatory rinses, topical anaesthetics<br>2 <sup>nd</sup> line: Topical sucralfate, aminosalicic acid, caustic solutions, oral tetracycline solutions, colchicine, levamisole, thalidomide, pulse methyl prednisolone, intralesional trimcinolone acetonide<br>3 <sup>rd</sup> line: Cyclosporine, azathiopurine, methotrexate, chlorambucil, infliximab, etanercept, plasmapheresis-apheresis, zinc sulphate, penicilline, azithromycin, minocycline, dapsone, pentoxifylline, interferon- $\alpha$  |
| Genital ulcers   | 1 <sup>st</sup> line: Topical triamcinolone acetonide, sucralfate, oral colchicine, azathiopurine, dapsone, prednisolone<br>2 <sup>nd</sup> line: Levamisole, interferon- $\alpha$ , methotrexate, thalidomide, cyclosporine A  |
| Papulopustular eruptions                                 | 1 <sup>st</sup> line: Topical bethametasone, oral colchicine, azathiopurine, dapsone, prednisolone<br>2 <sup>nd</sup> line: Levamisole, dapson, interferon- $\alpha$ , , thalidomide, azitromycin, pentoxifylline   |
| Erythema nodosum   | 1 <sup>st</sup> line: Oral colchicine, dapsone, prednisolone<br>2 <sup>nd</sup> line: Indomethacin, Dapson, interferon- $\alpha$ , thalidomide, azithromycin, erythromycin  |
| Articular involvement                                    | 1 <sup>st</sup> line: Indomethacin, oxaprozin, analgesics and the other nonsteroid antiinflammatory drugs, sulphasalazine, azathiopurine, oral colchicine, prednisolone, intrarticular triamcinolone acetonide injections and arthrocentesis.<br>2 <sup>nd</sup> line: Methotrexate, dapson, interferon- $\alpha$ , thalidomide, cyclosporin A, azathiopurine + cyclosporin A<br>3 <sup>rd</sup> line: DMARDs, serotonin reuptake inhibitors, amitriptyline   |
| Central nervous system involvement                       | 1 <sup>st</sup> line: Oral corticosteroids + azathiopurine, pulse iv methyl prednisolone, oral prednisolone<br>2 <sup>nd</sup> line: Oral or pulse iv cyclophosphamide, chlorambucil, methotrexate, azathiopurine   |
| Cardiovascular disease, arteritis, and venous thrombosis | 1 <sup>st</sup> line: Oral or pulse iv cyclophosphamide, azathiopurine, pulse iv methyl prednisolone, oral prednisolone, aspirin, sc or iv heparin, oral or iv warfarin, i.v. streptokinase<br>2 <sup>nd</sup> line: Dipyridamol, corticosteroid + cyclophosphamide.<br>3 <sup>rd</sup> line: Surgery, percutaneous transluminal angioplasty, cyclosporine A  |
| Thoracic involvement                                     | 1 <sup>st</sup> line: Oral prednisolone + pulse iv cyclophosphamide<br>2 <sup>nd</sup> line: Pulse iv corticosteroid + pulse iv cyclophosphamide<br>3 <sup>rd</sup> line: Anti-TNF agents   |
| Epididimoorchitis  | 1 <sup>st</sup> line: Oral prednisolone, colchicine, nonsteroid antiinflammatory drugs<br>2 <sup>nd</sup> line: Cyclosporine A  |
| Uveitis  | 1 <sup>st</sup> line: Topical corticosteroids eye-drops and ointments, mydriatics/cycloplegics, $\beta$ -blockers, $\alpha_2$ -agonists, oral colchicine, oral prednisolone, cyclosporin A, azathiopurine, intravitreal and parabolbar sub-Tenon capsule injections.<br>2 <sup>nd</sup> line: Pulse iv methyl prednisolone, oral methotrexate, carbonic anhydrase inhibitors, chlorambucil, topical NSAIDs<br>3 <sup>rd</sup> line: Infliximab, etanercept, interferon- $\alpha$ , thalidomide, Tacrolimus, corticosteroids + cyclophosphamide, azathiopurine + colchicine, corticosteroids + cyclophosphamide + azathiopurine, i.v. immunoglobulins, plasmapheresis, granulocytopheresis, mycophenolate mofetil. |
| Gastrointestinal involvement                             | 1 <sup>st</sup> line: Sulfasalazine, corticosteroids<br>2 <sup>nd</sup> line: Cyclosporine A, azathiopurine, surgery<br>3 <sup>rd</sup> line: Intraarterial corticosteroids injections  |
| Renal involvement  | 1 <sup>st</sup> line: Corticosteroids, azathiopurine, cyclophosphamide, cyclosporine<br>2 <sup>nd</sup> line: Peritoneal hemodialysis, renal surgery and renal transplantation  |

# Yeni Tedavi Seçenekleri

- Alemtuzumab (anti-CD52 MK-BH, göz, vasküler, SSS), Daklizumab (anti-IL-2-Tac/CD25, göz), hematopoietik kök hücre nakli, azasitidin (OÜ, GIÜ), ustekinumab, iksekizumab, bevakizumab (VEGF antagonistisi), sekukinumab, brodalumab, JAK-inh (Tofasitinib) dirençli BH için denenmektedir.

Endo M, Sekikawa A, Tsumura T, Maruo T, Osaki Y. Am J Case Rep. 2015;16:827-31

Mohammad AJ, Smith RM, Chow YW, Chaudhry AN, Jayne DR. J Rheumatol. 2015;42(10):1906-13

Buggage RR, Levy-Clarke G, Sen HN, Ursea R, Srivastava SK, Suhler EB, Altemare C, Velez G, Ragheb J, Chan CC, Nussenblatt RB, Bamji AT, Sran P, Waldmann T, Thompson DJ. Ocul Immunol Inflamm. 2007;15(2):63-70.

Nakamura Y, Matsuguma M, Tokunaga Y, Yamamoto K, Tanaka M, Tanaka Y, Yujiri T, Tanizawa Y. Intern Med. 2017;56(10):1199-1202.



# Teşekkürler:😊))

