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İSTANBUL BİLİM ÜNİVERSİTESİ

COLCHICINE IN BEHÇET DISEASE

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DEPARTMENT OF DERMATOLOGY

JEADV (2001) 15, 126–136

ORIGINAL ARTICLE

The multiple faces of Behçet's disease and its aetiological factors

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- Professor Hulusi Behçet defined a syndrome in 1937
  - Recurrent oral ulcers, genital ulcers and hypopyon uveitis by an unknown aetiology
- Behçet disease (BD) is a chronic multisystem disease
- There is an abnormal immune response triggered by an agent in patients with a genetic predisposition
- Presents as variable organ involvement and clinical features

- BD is endemic in the eastern Mediterranean, Middle and Far East (Silk Road) countries
- The highest prevalence is reported in Turkey
- Male/female ratio: 3 : 2.5
- The onset is in the 30's, it is rarely seen in children
- BD has a more aggressive course in young males

- *Önder M, Gürer MA. The multiple faces of Behçet's disease and its aetiological factors. EADV (2001) 15, 126 – 136.*
- *Tüzün Y, Yurdakul S, Mat C et al. Epidemiology of Behçet's syndrome in Turkey. Int J Dermatol 1996;35:618–620.*

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Vol. 44, No. 11, November 2001, pp 2686–2692

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A Double-Blind Trial of Colchicine in Behçet's Syndrome

Sebahattin Yurdakul, Cem Mat, Yalçin Tüzün, Yilmaz Özyazgan, Vedat Hamuryudan, Ömer Uysal, Mustafa Şenocak, and Hasan Yazici

- Behçet disease is a systemic vasculitis of unknown etiology located in small and large vessels
- It is characterized by variable clinical features
  - Recurrent oral ulceration in almost all patients
  - Frequent genital ulcers
  - Skin lesions
  - Arthritis, panuveitis, thrombophlebitis, GI disease, CNS involvement

Yazici H, Yurdakul S, Hamuryudan V. Beh¸cet's syndrome. In: Maddison PJ, Isenberg DA, Woo P, Glass DN, editors. Oxford textbook of rheumatology. Second ed. Oxford, UK: Oxford University Press; 1998. p. 1394–1402.

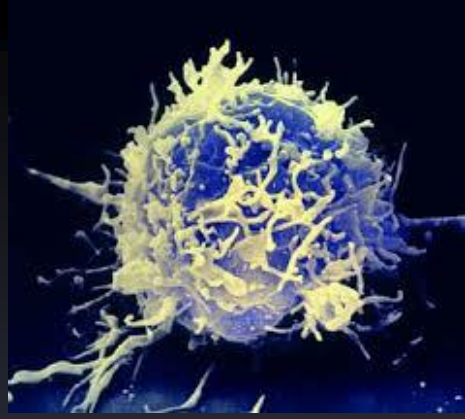
Recurrent oral ulceration	Minor aphtous, major aphtous or herpetiform ulceration observed by physicion or patient, which recurred at least 3 times in a year
Plus 2 of the fallowing criteria:	
Recurrent genital ulceration	Aphtous ulceration or scarring observed by physician or patient
Eye lesions	Anterior uveitis, posterior uveitis or cells in vitreous on slit lamp examination or retinal vasculitis observed by ophtalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions or acneiform nodules observed by physician in postadolescent patients not on corticosteroid traetment
Positive pathergy test	Read by physician at 24-48 h

International Study Group of Behçet's disease. Criteria for diagnosis of Behçet's disease. Lancet 1990; 335: 1078 –1080.

- The treatment of BD is based on clinical manifestations
- Topical treatments reduce pain, help the healing process
- Systemic therapy is indicated in severe mucocutaneous BD
  - Colchicine, dapsone, non-steroidal anti-inflammatory drugs, corticosteroids, thalidomide, penicillin, IFN-α, azathioprine, methotrexate, cyclosporine

- *Önder M, Gürer MA. The multiple faces of Behçet's disease and its aetiological factors. EADV (2001) 15, 126 – 136.*
- *Yazıcı H, Yurdakul S, Hamuryudan V. Behçet's syndrome. How should we treat it? Clin Immunother 1995; 2: 102–107.*

- Colchicine is a toxic natural product derived from the plant Colchicum autumnale (autumn crocus or meadow saffron)
- Colchicine, was first isolated in 1820 by the two French chemists P.S. Pelletier and J. Caventon
- Its effect derives from inhibition of leukocyte chemotaxis
- Colchicine interferes with the growth of microtubules in cells

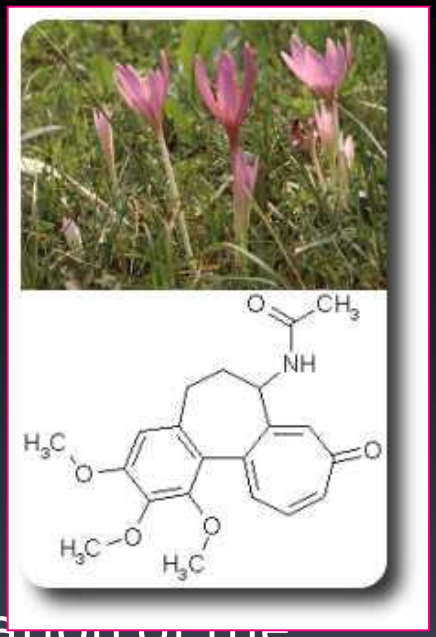


Anti-mitotic

Anti-inflammatory

- Reduces mobility, adhesiveness, chemotaxis of polymorphonuclear cells
- Inhibits T-lymphocyte activation
- Increases collagenase production,promotes collagenolysis

- *Cronstein BN, Molad Y, Reibman J et al. Colchicine alters the quatitative and qualitative display of selectins on endothelial cells and neutrophils. J Clin Invest 1995;96:994-1002.*
- *Perico N, Ostermann D, Bontempeill M, et al. Colchicine interferes with L-selectin and leukocyte function-associated antigen-1 expression on human T lymphocytes and inhibits T cell activation. J Am Soc Nephrol 1996;7:594-601.*



Immunosuppressive action

- Inhibits cell-mediated immune response

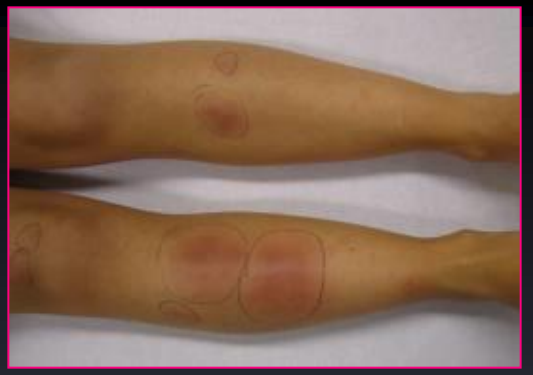
Other pharmacological effects

- Blood vessel contraction, hypertension, modification of the neuromuscular function

Mekori YA, Baram D, Goldberg A, Klajman A. Inhibition of delayed hypersensitivity reactions in mice by colchicine. I. Mechanism of inhibition of contact sensitivity in vivo. Cell Immunol 1989;120:330-40.

- It must be protected from sunlight
- It is rapidly absorbed after oral intake
- Peak plasma levels are reached in 30 and 120 minutes
- It is metabolized in the liver, 80% is eliminated through feces
- 10-20% is eliminated in the urine

Konda C, Rao AG. Colchicine in dermatology. Indian J Dermatol Venereol Leprol 2010;76:202-6.



- The efficacy is not the same in male and female patients
- Significant beneficial effects on erythema nodosum and genital lesions were observed in women
- Colchicine was effective for arthritis in both sexes
- HLA status is not influential in response to colchicine

Yurdakul S, Mat C, Tüzün Y, et al. A Double-Blind Trial of Colchicine in Beh¸cet's Syndrome. ARTHRITIS & RHEUMATISM Vol. 44, No. 11, November 2001, pp 2686–2692

- No definite effect is noted on oral ulcerations in either sex
- The use of colchicine is limited to patients with mild mucocutaneous lesions
- In a 6-month controlled study, it was found to be effective in erythema nodosum and arthralgia

Yurdakul S, Mat C, Tüzün Y, et al. A Double-Blind Trial of Colchicine in Beh¸cet's Syndrome. ARTHRITIS & RHEUMATISM Vol. 44, No. 11, November 2001, pp 2686–2692

- 116 patients with mucocutaneous BD received either placebo or colchicine (1–2 mg/day) in a double-blind trial for 2 years
- Significant response was observed in genital ulcers , erythema nodosum , and arthritis among women
- Occurrence of arthritis was reduced among male patients
- Adverse effects were similar in both groups

Yurdakul S,Mat C, Tüzün Y, et al. A Double-Blind Trial of Colchicine in Beh¸cet's Syndrome. ARTHRITIS & RHEUMATISM Vol. 44, No. 11, November 2001, pp 2686–2692

REVIEW ARTICLE

Drugs 2012; 72 (17): 2223-2241
0012-6667/12/0017-2223/$55.50/0

Behcet's Syndrome

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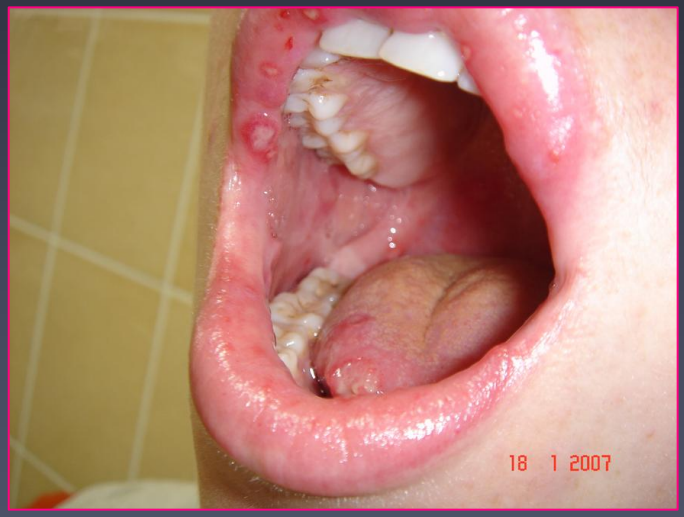
Oral/Genital Ulcers

- Initial treatment for ulcers are:
  - Topical steroids, 3-4 times daily
  - Anaesthetic agents
  - Sucralfate
- If ineffective, colchicine daily, with cs 5-15 mg/day

- For refractory disease:
  - Azathioprine 2,5mg/kg/day or TNF-α inhibitors
- For EN associated with BD more aggressive immunosuppression is needed
- Prednisolone (20-60 mg daily) with azathioprine (2.5mg/kg/day) over 2 months

- A study by Aktulga et al did not show any significant effect of colchicine for oral ulcerations
- There was a significant reduction in both genital ulcers and EN in female patients



Aktulga E, Altac M, Muftuoglu A, et al. A double-blind study of colchicine in Behcet's disease. Haematologica 1980 Jun; 65 (3): 399-402

- Davatchi et al. evaluated the efficacy of colchicine in a double- blind, placebo-controlled trial
- Patients in the colchicine arm showed improvement in total disease activity, orogenital ulcers, pseudofollicular lesions and EN

Davatchi F, Sadeghi Abdollahi B, Tehrani Banihashemi A, et al. Colchicine versus placebo in Behcet's disease; ran- domized, double-blind, controlled crossover tdal. Mod Rheumatol 2009; 19 (5): 542-9

Gül A. Standard and Novel Therapeutic Approaches to Behç et's Disease. Drugs 2007; 67 (14): 2013-2022

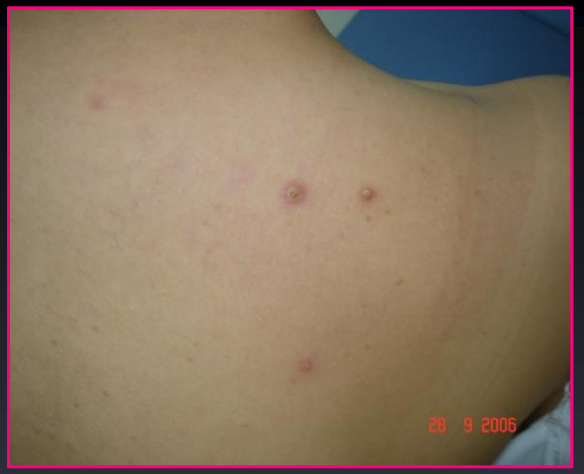
Table III. Drugs assessed in randomised controlled trials for use in Behçet's disease

Drug	Dose	Manifestation	Duration	Comparator	Result	Reference
Ciclosporin	10 mg/kg	Eye involvement	16wk	Colchicine	Favourable	19
Azathioprine	2.5 mg/kg	Eye involvement	2y	Placebo	Favourable	18
Colchicine	0.5mg tid	Oral aphthous ulcers, and others	24wk	Placebo	No efficacy	20
	1–2 mg/day	Mucocutaneous, articular	2y	Placebo	Favourable	14
Thalidomide	100 or 300 mg/day	Mucocutaneous	24wk	Placebo	Favourable	21
Dapsone	100 mg/day	Mucocutaneous	3mo	Placebo	Favourable	22
Methylprednisolone	40 mg/every 3wk	Mucocutaneous	27wk	Placebo	Favourable for erythema nodosum	23
Aciclovir	4000 mg/day for 1wk, then	Mucocutaneous	12wk	Placebo	No efficacy	24
	800 mg/day for 11wk					
Azapropazone	300mg tid	Articular	3wk	Placebo	No efficacy	25
Benzathine-benzylpenicillin plus colchicine	1.2 MIU/mo	Articular	24mo	Colchicine	Favourable	26
Rebamipide	300 mg/day	Oral aphthous ulcers	12–24wk	Placebo	Favourable	27
Sucralfate	Topical, qid	Mucocutaneous	3mo	Placebo	Favourable	28
Interferon-α-2a	2 MIU, 3/7 days	Mucocutaneous, articular	3mo	Placebo	Favourable	29
Interferon-α-2c	Topical, 10^5 U/g qid	Oral aphthous ulcers	24wk	Placebo	No efficacy	30
Etanercept	25mg, twice a week	Pathergy, skin, arthritis	4wk	Placebo	No efficacy on pathergy Favourable for oral ulcers and nodular lesions	31

bid = twice daily; **qid** = four times daily; **tid** = three times daily.

- Two studies were conducted with colchine versus colchicine + benzadine penicillin in 120 Behçet disease patients
- The combination therapy arm was found to be more effective in patients with mucocutaeous disease
  - Oral ulcerations, geninal ulcerations, erythema nodosum

- *Çalgüneri et al. Effect of prophylactic benzathine penicillin on mucocutaneous symptoms of Behçet's disease. Dermatology1996; 192: 125-8*
- *Al-Waiz MM ve ark, Colchicine and benzathine penicilin in the treatment of Behcet disease: a case comparative study. Dermatol Online J. 2005:*



- Colchicine is useful for treating arthritis and mucocutaneous manifestations of BD
- Female patients respond better to colchicine
- *Limiting the use of colchicine to the treatment of erythema nodosum and genital lesions seen mainly among the female patients can be recommended*

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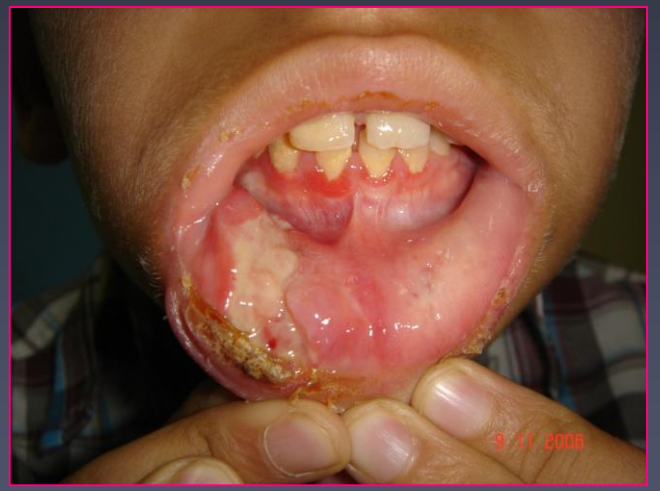
- Colchicine is an alkaloid administered orally (0.5–2mg/d)
- Colchicine is usually well tolerated
- GI adverse effects are the most frequent
  - Diarrhea, nausea, vomiting, abdominal pain



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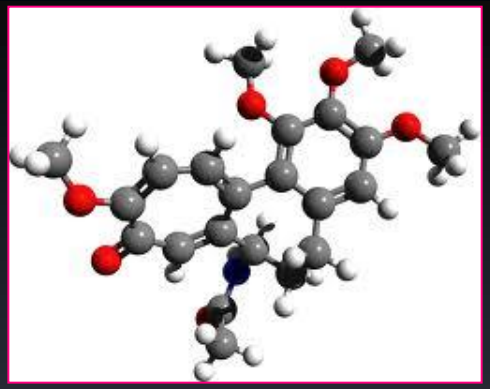
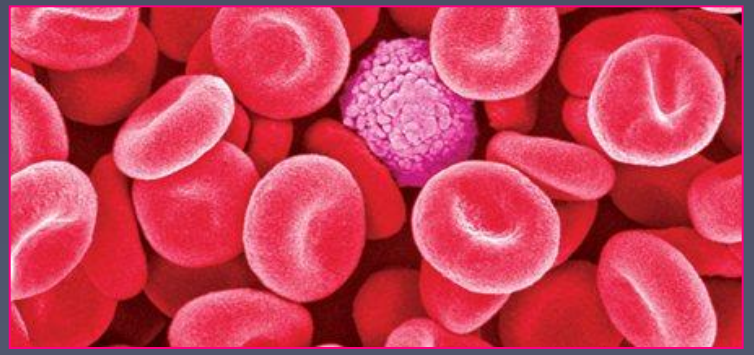


- The GI side effects are due to:
  - Increase in gut motility by neural mechanisms
  - Inhibition of mitosis in mucosa
- Symptoms decrease on reducing the dose
- Long-term therapy may cause steatorrhea, malabsorption

- Malabsorption of vit B12 may lead to megaloblastic anemia
- Prolonged treatment:
  - Bone marrow suppression, agranulocytosis, thrombocytopenia, aplastic anemia
- Colchicine-induced leukopenia occurs with overdose
- G-CSF must be considered in leukopenia



- Myopathy and neuropathy can occur in renal deficiency
- Coadministration of simvastatin may induce myopathy
- Myopathy:
  - Proximal muscle weakness, rise in creatinine phosphokinase, abnormal proximal muscle fibrillations
  - Myopathy improves after withdrawal

- Neuropathy resolves in a longer period of time
- Azoospermia is a reported side effect
- Dermatological adverse effects:
  - Urticaria, TEN, porphyria cutanea tarda induction
  - Alopecia areata, 2-3 weeks after the onset of therapy, involving face, axilla, pubis

- The coadministration of colchicine and cytochrome P450 3A4 inhibitors may inhibit its metabolism resulting in toxicity
  - Macrolide antibiotics
- Colchicine may increase serum concentration of cyclosporine and verapamil

COLCHICINE MONITORING

- Complete blood count, platelet count, serum renal and liver function tests, and urine analysis:
  - Every month for the first 3 months
  - Every 3 months during the treatment
- Colchicine should not be used during pregnancy

- BD draws the attention of clinicians worldwide
- Management of BD has progressed considerably with the help of evidence-based guidelines
- More information on pathogenesis of BD also contributed to our treatment approach

- Large, multicenter trials are still needed to increase our understanding of BD
- Newer therapeutic agents and methods are currently under investigation to further help the disease control
  - Rituximab, alemtuzumab, haematopoetic stem cell transplantation