COLCHICINE IN BEHÇET DISEASE

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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

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent oral ulceration</td>
<td>Minor aphtous, major aphtous or herpetiform ulceration observed by physician or patient, which recurred at least 3 times in a year</td>
</tr>
<tr>
<td>Plus 2 of the following criteria:</td>
<td></td>
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<tr>
<td>Recurrent genital ulceration</td>
<td>Aphtous ulceration or scarring observed by physician or patient</td>
</tr>
<tr>
<td>Eye lesions</td>
<td>Anterior uveitis, posterior uveitis or cells in vitreous on slit lamp examination or retinal vasculitis observed by ophthalmologist</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions or acneiform nodules observed by physician in postadolescent patients not on corticosteroid treatment</td>
</tr>
<tr>
<td>Positive pathergy test</td>
<td>Read by physician at 24-48 h</td>
</tr>
</tbody>
</table>

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.


• 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


Immunosuppressive action

• Inhibits cell-mediated immune response

Other pharmacological effects

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

• 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

• 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

• 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

• 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

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

• 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

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

*bid = twice daily; qid = four times daily; tid = three times daily.*
• Two studies were conducted with colchicine versus colchicine + benzadine penicillin in 120 Behçet disease patients
• The combination therapy arm was found to be more effective in patients with mucocutaneous disease
  – Oral ulcerations, genital ulcerations, erythema nodosum


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

• 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

• 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, haematopoietic stem cell transplantation