Editorial

Evidence-based treatment of Behçet's syndrome

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Received on July 3, 2006; accepted on July 5, 2006.

Clin Exp Rheumatol 2006; 24 (Suppl. 42): S53-S55.

Key words: Behçet's syndrome, colchicine, azathioprine, entanercept, methylprednisolone.

The treatment of Behçet's syndrome (BS) is directed by the type and severity of symptoms. Elderly patients and females have a generally mild disease course while both mortality and morbidity related to eye, vascular and neurological diseases are increased among the young and the males (1); the rationale of more aggressive therapy in this group. I critically review only the 12 double-blind, randomized controlled systemic drug trials, excluding those with topical agents, in a historical perspective (Table I).

Transfer factor against placebo was the first controlled study (2). Results with transfer factor and then acyclovir (4) were not beneficial suggesting that immunologic disturbances and herpes simplex virus infection were not operative in the pathogenesis. However, in both of these crossover trials, durations were short (6 and 3 months, respectively) and the number of patients were limited (n = 20 and n = 22, respectively). Furthermore they mainly had mucocutaneous lesions. The patients were also older (mean age 43, range: 18 - 55) and were predominantly females in the acyclovir study.

Earlier open studies had claimed that colchicine in BS was beneficial for every lesion. However, in 1980 our group completed the first controlled drug study with colchicine against placebo in a double blind manner (to the best of our knowledge, the first double-blind study of any kind in Turkey) among 35 patients, in mainly males for 6 months (3). This trial showed that colchicine was useful only for erythema nodosum and arhtralgia. As males have more severe disease than females, we were able to do a 2 year placebo controlled study with colchicine among both genders 21 years later (9). The study patients were young (18 - 35 years), the disease duration was short (≤ 2 years), and all had active mucocutaneous lesions, defined as the minimum presence of oral or genital ulcers or erythema nodosum occurring at least three times within the preceding six months. When analyzed separately for each sex, colchicine 1-2 mg/day was found to be useful for genital ulcers, erythema nodosum, and arthritis among women but only for arthritis among men.

Cyclosporin 10 mg/kg versus colchicine 1 mg was investigated in 96 patients with at least 2 ocular attacks within the preceding 16 weeks for 16 weeks and a visual acuity of 20/40 or less (5). It was reported that cyclosporin was more effective for reducing the frequency and severity of ocular attacks, and that it improved visual acuity compared with colchicine. Cyclosporin decreased the mucocutaneous lesions such as aphthous ulcers, dermal lesions, and genital ulcers as well. Neither patient's characteristics such as mean age, sex distribution, and disease duration at entry nor the mean numbers of ocular attacks and mucocutaneous lesions throughout the study were given. Furthermore, colchicine resistant patients were probably randomized again. At this dosage of cyclosporin (10 mg), hirsutism and renal dysfunction (n = 23 vs n = 2 and n = 11 vs n = 2, $p < 0.05$ for both) were the main side effects compared to colchicine. Therefore, it is contemporarily used at 5 mg/kg. Cyclosporin acts promptly and is beneficial for sight threatening and progressive uveitis, especially with retinal vasculitis. However, close monitoring is required for hypertension, nephrotoxicity, and neurotoxicity even at this dose.

Azathioprine 2.5 mg/kg/day, was studied for eye and mucocutaneous lesions (6). Only male patients were included in the study. The study groups were a) patients without eye involvement, disease duration ≤ 2 years, and aged < 40

Table I. Double-blind, randomized controlled systemic drug trials in Behçet's syndrome.

Study drugs, duration, and year	Patient numbers and selection	Comments
Transfer factor *vs* P, 6 months cross-over, 1979	20 (11 M / 9 F), MC lesions	No benefits for disease course.
Colchicine 0.5 mg tid *vs* P, 6 months, 1980	35, MC lesions	First double blind trial with colchicine. It is useful for *e. nodosum* and arthralgia.
Acyclovir 4 g then 800 g/day *vs* P, 12 wks crossover, 1988	22 (7 M / 15 F), MC lesions	No differences in the frequencies of oro-genital lesions between groups.
Cyclosporin 10 mg/kg/day *vs* colchicine 1 mg,16 wks,1989	96, active eye disease	Cyclosporin is more effective on eye and mucocutaneous lesions compared to colchicine.
Azathioprine, 2.5 mg/kg/day *vs* P, 2 years, 1990	73 M (48 with and 25 without eye disease)	Effective for preserving visual acuity and preventing the emergence of new eye disease. Beneficial in mucocutaneous lesions and arthritis.
Azapropazone 300mg tid *vs* P, 3 wks, 1995	63, acute arthritis	Not different from placebo on arthritis.
Thalidomide 300 and 100 mg day *vs* P, 24 wks, 1998	96 M, active MC lesions	Thalidomide at both dosages is effective for oral and genital ulcers and follicular lesions.
Colchicine 1-2 mg day *vs* P, 2 years, 2001	116 (60 M / 56 F), active MC lesions	Effective in genital ulcers, e. nodosum and arthritis in females but only in arthritis in males.
Dapsone 100 mg day *vs* P, 3 months cross-over, 2002	20, (16 M / 4 F), MC lesions	Favourable effect on mucocutaneous lesions
IFN-α-2a 6 MU 3 times weekly *vs* P, 3 months, 2002	50 (31 M / 19 F), MC lesions	Favourable effect on orogenital ulcers and papulopustular lesions.
Etanercept 25 mg SC 2 times weekly *vs* P, 4 wks, 2005	40 M, pathergy and monosodium urate positive, MC lesions	No effect on pathergy and monosodium urate tests but effective for oral ulcers, nodular and papulopustular lesions.
Methylprednisolone 40 mg IM/three weekly *vs* P, 27 wks, 2006	86 (43 M / 43 F), active genital ulcers	Not effective for genital, oral ulcerations, folliculitis, and arthritis. Effective for e. nodosum among the females but not in males.

P: Placebo; M: male; F: female; MC: mucocutaneous; e.nodosum: erythema nodosum; wks: weeks

years (n = 25), and b) patients with eye involvement and any age and disease duration (n = 48). This 2 year controlled study showed that all 6 patients due to severe eye disease withdrawn from the study were in the placebo group ($p < 0.001$). Azathioprine was significantly effective for the prevention of new eye disease both in group a (n = 1 vs. n = 8, $p < 0.01$) and progression in the unaffected eye (n = 0 vs n = 5, $p < 0.001$) in group b among the 14 patients with unilateral eye disease at entry. Group b had less attack of hypopyon uveitis (n = 1 with one episode vs. n = 7 with 15 episodes, $p < 0.001$). Patients taking azathioprine also had significantly less frequent oral and genital ulcers and arthritis as well. In addition, there was a trend for preventing deep vein thrombosis ($\chi^2 = 2.90$, $0.10 > p > 0.05$). However, no conclusions could be withdrawn for less frequent lesions such as gastrointestinal and neurological manifestations as the numbers of these events were too few. There were no serious side effects attributable to azathioprine. In current clinical practice azathioprine is usually underdosed, the proper dose we maintain, being 2.5 mg/kg/day. Furthermore, at least three months is required for a beneficial response.

We formally tested a nonsteroidal anti-inflammatory drug, azapropazone 300 mg tid for three weeks in 63 patients with acute arthritis of up to 10 days duration (7). At the end of trial there were no significant differences between the azapropazone and placebo groups. The arthritis persisted in nearly half of the patients and the duration of arthritis was 19 days in both arms. Additionally, new arthritis developed in 21% of patients in the azapropazone and in 31 % of patients in the placebo groups. The degree of joint swelling, the tender joint score and VAS for pain significantly improved in both groups. There were also no differences in the number of analgesics used, or in the CRP and ESR levels between groups. We concluded that azapropazone was not effective for acute arthritis of BS.

Thalidomide, 100 mg and 300 mg daily against placebo, was studied for the oral and genital ulcers in a 24 week trial in only male patients (n = 96, aged 18 - 35). All had active mucocutaneous lesions defined as occurrence of at least two attacks of oral or genital ulcerations within the preceding 3 months without major organ involvement (8). Oral or genital ulceration were totally absent in 2 patients in the thalidomide 100 mg and 5 patients in the thalidomide 300 mg, whereas there were no patients without them in the placebo groups ($p = 0.001$). Either dose of thalidomide also decreased significantly the mean numbers of oral and genital ulceration, and follicular lesions. However, the drug resulted in significant increases in erythema nodosum lesions compared with placebo during the first 2 months. Polyneuropathy developed in one patient in the thalidomide 100 mg and in 3 patients in the thalidomide 300 mg groups. In clinical practice, the use of thalidomide is limited by side effects such as polyneuropathy, terato-

genesis, and sedation.

A controlled trial with dapsone 100 mg/day against placebo showed that the drug was beneficial for mucocutaneous lesions. However the number of patients was limited (n = 20) (10).

Interferon (INF) α-2a, subcutaneously, 6 MU three times a week for 3 months was tested against placebo in 50 patients with mainly mucocutaneous lesions (11). INF significantly decreased the duration and pain of oral ulcers and the frequency of genital ulcers and papulopustular lesions compared with those observed in the pre-treatment period. All symptoms recurred during the post treatment follow up. Side effects were fever, arthralgia, injection site reactions, leucopenia, alopecia and depression. Unfortunately, information on the numeric evaluation on the improvement of various organ systems is not available.

There are case reports or small series with TNF blocking agents with success. The only placebo controlled study with this family of drugs was done with etanercept again by our group (12). Only males (n = 40) with positive pathergy and monosodium urate tests were equally randomised to placebo or etanercept 25 mg twice a week for 4 weeks. Etanercept did not the affect the pathergy and monosodium urate tests while it significantly decreased the mean numbers of oral ulcers, nodular and papulopustular lesions. The probability of being free of oral ulcers and nodular lesions was higher in the etanercept group compared with the placebo ($p = 0.0017$ and $p = 0.0002$, respectively) as well.

Corticosteroids are widely used for BS but no controlled data are available. We have recently tested the efficacy of depot corticosteroids in a double blind placebo controlled study for genital ulcers of BS (13). Forty three females and 43 male patients, who had active genital ulcers defined as at least one genital ulcer within the preceding six months, were separately randomised to receive either intramuscular injection of 40 mg methylprednisolone acetate or placebo every three weeks for 27 weeks. Each gender was analyzed separately. There were no significant differences in the mean number of genital ulcers, oral ulcerations, folliculitis, and arthritis. However, depot corticosteroids were useful in controlling only erythema nodosum lesions among the females ($p = 0.0148$) but not in males ($p = 0.1$). This beneficial effect among the females disappeared during the 2-month post treatment follow-up.

Although double blind controlled studies have increased our knowledge in using classical drugs during the recent years we do not know the best treatment of thrombophlebitis, neurological, gastrointestinal, and arterial involvement. Therefore, formal controlled studies are urgently needed. Moreover, head to head comparisons of TNF antagonists and IFN with more traditional drugs such as cyclosporine are required.

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