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Correction of a suppressor cell deficiency in four patients with familial Mediterranean fever by *in vitro* or *in vivo* colchicine

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SUMMARY

We have previously reported that three patients with familial Mediterranean fever (FMF) had deficient concanavalin A (Con A) activated suppressor cell inhibition of the proliferation of healthy volunteers' phytohaemagglutinin stimulated responder cells. When these three FMF patients were treated with long term oral colchicine (2 mg/day), their Con A activated suppressor cell deficiency was corrected and FMF attacks prevented. In the present report, the effect of *in vitro* as well as *in vivo* colchicine treatment on the suppressor cell function of these three FMF patients as well as one more FMF patient was tested to determine whether colchicine can directly increase suppressor cell function rather than colchicine's preventing FMF attacks by unknown mechanisms which only indirectly results in a correction of the suppressor cell deficiency. Long term oral colchicine treatment corrected the suppressor cell deficiency in the four FMF patients ($5 \pm 2\%$, $35 \pm 5\%$, and $46 \pm 4\%$ for mean $\pm$s.e.m. % suppression for 0, 1 and 2 mg/day of oral colchicine, respectively). Oral colchicine treatment corrected their suppressor cell deficiency within one week of commencing treatment and even corrected one of the FMF patient's suppressor cell deficiency while he still had some FMF attacks on 1 mg/day of colchicine. Suppressor cells from two of the *in vivo* untreated FMF patients cultured with 10^{-5} M colchicine plus Con A significantly ($P < 0{\cdot}01$) suppressed proliferation ($36 \pm 5\%$) as compared to their suppressor cells cultured only with Con A ($4 \pm 7\%$). Furthermore, these *in vivo* untreated FMF patients' suppressor cells cultured with 10^{-5} M colchicine (without Con A) often suppressed as compared to their suppressor cells cultured in medium. Thus colchicine appears to directly correct these FMF patients' suppressor cell deficiency. These observations raise the possibility that colchicine may be therapeutically useful in treating patients with other diseases associated with an absolute or relative deficiency of suppressor cell function.

INTRODUCTION

We have previously reported that four familial Mediterranean fever (FMF) patients from one family (proband, proband's father, proband's brother and proband's first son [referred in our previous publications as proband's son]) had a defect in the ability of their Con A activated suppressor cells to inhibit the proliferation of phytohaemagglutinin (PHA) stimulated responder cells from healthy volunteers (Ilfeld, Weil & Kuperman, 1980, 1981a). When the proband's father,

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brother, and first son were treated with long term oral colchicine (2 mg/day), their *in vitro* suppressor cell deficiency was corrected and their FMF attacks prevented (Ilfeld *et al.*, 1981b). The critical question was whether colchicine directly corrected these FMF patients' suppressor cell deficiency (and thus might be therapeutically useful in treating patients with other diseases associated with a suppressor cell deficiency) or colchicine prevented FMF attacks by unknown mechanisms which then only indirectly resulted in a correction of their suppressor cell deficiency.

The present report describes the effect of *in vitro* and *in vivo* colchicine treatment on suppressor cell function of these three FMF patients and the proband's second son with FMF. Evidence is presented which suggests that *in vitro* colchicine as well as *in vivo* colchicine treatment directly corrected these FMF patients' Con A activated suppressor cell function.

MATERIALS AND METHODS

Patients. The clinical findings of the proband and his father, brother and first son with FMF have already been described (Ilfeld *et al.*, 1981c, 1982a). The proband's second son with FMF (age 5) had 11 attacks of fever, abdominal pain and joint pain for 2–3 days' duration during 4 months before starting colchicine treatment. Whenever the proband's father, brother and two sons with FMF temporarily stopped colchicine treatment (against medical advice), they soon had attacks of fever and abdominal pain with or without joint pain for 1–3 days' duration.

Suppressor cell assay. Blood was always drawn from the FMF patients when they were clinically asymptomatic and their putative mononuclear suppressor cells (pre-cultured for 44 hr with or without 10 μg/ml of Con A (Miles Yeda, Rehovot, Israel) and/or 10^{-5} M colchicine (Sigma, St Louis, Missouri, USA)) were tested for the ability to inhibit the proliferation of PHA stimulated responder mononuclear cells from healthy volunteers as previously described (Ilfeld *et al.*, 1981a). Percentage suppression of tritiated thymidine uptake was calculated according to the following formula where RC and SC represent responder cells and suppressor cells, respectively.

$$\% \text{ suppression} = \left(1 - \frac{(\text{c.p.m. (PHA} + \text{RC} + \text{SC)} - \text{c.p.m. (RC} + \text{SC))}}{(\text{c.p.m. (PHA} + \text{RC)} - \text{c.p.m. RC)}}\right) \times 100\%$$

Statistical significance was calculated by the two tailed Student's *t*-test.

RESULTS

Twenty-nine healthy volunteers were tested in a total of 37 assays with a mean (±s.e.m.) Con A activated suppressor cell function of 45±2%. Decreased levels of Con A activated suppressor cell function were defined as a percentage suppression more than two standard deviations below the mean of the healthy volunteers (19%). All nine of the proband's first degree healthy family members (proband's brother, two sisters, three sons and three daughters) and all five of the proband's more distantly related healthy family members tested had normal levels of Con A activated suppressor cell function (49±4%). In contrast, the four untreated FMF patients (each tested three or four times between FMF attacks when they were clinically asymptomatic) had significantly ($P < 0.001$) decreased Con A activated suppressor cell function (father 9±4%, brother 2±2%, first son 8±3%, and second son 12±2%) as compared to the healthy volunteers and healthy family members.

The two adult FMF patients (proband's father and proband's brother) were started on colchicine 1 mg twice daily which significantly ($P < 0.01$) increased their suppressor cell function to 37% and 47% (respectively) and prevented FMF attacks (see Fig. 1 for the proband's father). The father and brother decreased their dose of colchicine to 1 mg once daily (in order to fast during the Moslem month of Ramadan) and their suppressor cell function decreased to 24% and 27%, respectively (without any FMF attacks). Thereafter, they increased the dose back to 1 mg twice daily of colchicine and their suppressor cell function increased to 44% and 35%, respectively.

The proband's first son with FMF was started on 0·5 mg twice daily of colchicine which reduced the severity of attacks and the frequency of attacks (from about 20 attacks in the previous 8 months

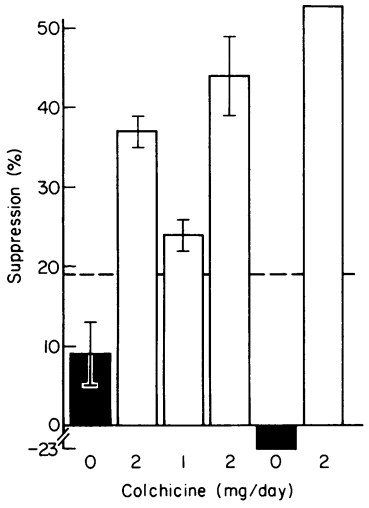

Fig. 1. Effect of oral colchicine treatment on the proband's father's Con A activated suppressor cell function. The proband's father was tested for Con A activated suppressor cell function when untreated (tested between FMF attacks), treated with 2, 1, and then 2 mg/day of colchicine (without FMF attacks), untreated (tested between FMF attacks), and then treated with 2 mg/day of colchicine (without FMF attacks). Results shown as mean (±s.e.m. when tested two or more times) percent suppression of proliferation of healthy volunteers' PHA stimulated responder cells. Recurrent FMF attacks (■). Absence of FMF attacks (□). The lower limit of normal (mean −2 standard deviations) for healthy volunteers' Con A activated suppressor cell function (19%) is shown by the horizontal dotted line.

without treatment to seven attacks during the 8 months of colchicine treatment). After 8 months of treatment with colchicine 0·5 mg twice daily, his Con A activated suppressor cells gave a mean of 51% suppression against two different healthy volunteers' PHA stimulated responder cells when tested 4 days after the end of an acute attack of fever, abdominal pain and joint pain. His dose of colchicine was then increased to 1 mg twice daily which totally prevented further FMF attacks and he continued thereafter with normal levels of suppressor cell function (57%).

The proband's second son with FMF was tested once, 10 months before the clinical onset of FMF attacks and he had a normal level of Con A activated suppressor cell function (26%) (Fig. 2). This very preliminary observation of normal suppressor cell function before the clinical onset of disease suggests that a suppressor cell deficiency may not be the primary genetic disorder of the five FMF patients from this particular family. After the onset of clinical disease, the proband's second son had decreased levels of Con A activated suppressor cell function when tested between FMF attacks when he was clinically asymptomatic. Treatment with 1 mg/day of colchicine corrected his suppressor cell deficiency and prevented FMF attacks. When the proband's father (Fig. 1) and the proband's second son (Fig. 2) temporarily discontinued oral colchicine treatment, they again had a suppressor cell deficiency and FMF attacks. Within 1 week of reinstituting oral colchicine treatment, they both had normal levels of Con A activated suppressor cell function.

Three of the FMF patients have been treated with oral colchicine for more than 2 years and the other FMF patient for more than 1 year. They have continued to have normal levels of suppressor cell function and no FMF attacks as long as the father, brother and first son take 1·5–2·0 mg/day of colchicine and the second son takes at least 1 mg/day of colchicine.

Blood was routinely drawn from the FMF patients about 12 hr after their last dose of colchicine. In one experiment, the proband's brother's blood was drawn 72 hr after his last dose of colchicine and his mean Con A activated suppressor cell function (25%) against two different responder cells was similar (in the same assay) to three untreated healthy volunteers (mean 28%) and the proband treated with maintenance haemodialysis and intermittent blood transfusions (30%). This sustained effect of oral colchicine treatment on suppressor cell function is consistent with Ertel & Wallace's (1971) observation of colchicine's long half-life in peripheral blood white cells.

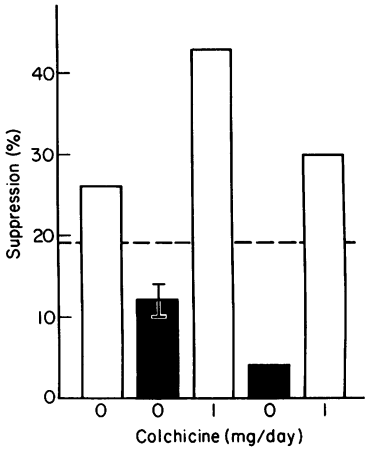

Fig. 2. Effect of oral colchicine treatment on the proband's second son's Con A activated suppressor cell function. The proband's second son was tested for Con A activated suppressor cell function when untreated (before the clinical onset of disease), untreated (tested between FMF attacks), treated with 1 mg/day of colchicine (without FMF attacks), untreated (tested between FMF attacks), and then treated with 1 mg/day of colchicine (without FMF attacks). Results shown as mean (±s.e.m. when tested two or more times) percent suppression of proliferation of healthy volunteers' PHA stimulated responder cells. Recurrent FMF attacks (■). Absence of FMF attacks (□). The lower limit of normal (mean −2 standard deviations) for healthy volunteers' Con A activated suppressor cell function (19%) is shown by the horizontal dotted line.

Table 1. Effect of *in vitro* and *in vivo* colchicine on suppressor cell function

Suppressor cells		Expt. 1. Father and second son without oral colchicine treatment			Expt. 2. Father and second son during oral colchicine treatment		
Donor	Incubation	Medium	PHA	% Suppression	Medium	PHA	% Suppression
—	—	218±21	31,710±1,265	—	216±23	24,566±1,481	—
Second son	Medium	322±20	36,773±3,549	−16	253±17	22,793±345	7
Second son	Colchicine	416±38	46,031±1,379	−45	253±25	20,184±1,386	18
Second son	Con A	357±28	30,574±1,290	4	368±25	17,294±528	30
Second son	Colchicine +Con A	329±27	22,710±1,940	29	462±13	19,249±1,361	23
Father	Medium	486±44	48,462±4,097	−52	477±79	23,118±503	7
Father	Colchicine	363±26	31,708±1,897	0	550±64	21,727±1,496	13
Father	Con A	418±19	39,184±1,905	−23	440±36	11,881±300	53
Father	Colchicine +Con A	404±60	25,194±1,861	21	335±29	14,467±748	42
Normal	Medium	391±22	31,295±1,539	2	349±30	20,968±1,446	15
Normal	Con A	453±19	21,245±1,778	34	393±36	16,262±483	35

The proband's father and the proband's second son with FMF were tested for suppressor cell function about 1 month after temporarily discontinuing oral colchicine treatment (Expt. 1). Each of them had already suffered three FMF attacks in the past month. They restarted oral colchicine treatment (father 2 mg/day, second son 1 mg/day) and their suppressor cell function was tested 1 week later (Expt. 2). Their suppressor cells were incubated with either medium, 10^{-5} M colchicine, Con A, or Con A plus 10^{-5} M colchicine. In each experiment, a healthy volunteer's suppressor cells were incubated with medium or Con A. The data represents the mean (±s.e.m.) c.p.m. of tritiated thymidine uptake by a freshly drawn healthy volunteer's unstimulated or PHA stimulated responder cells.

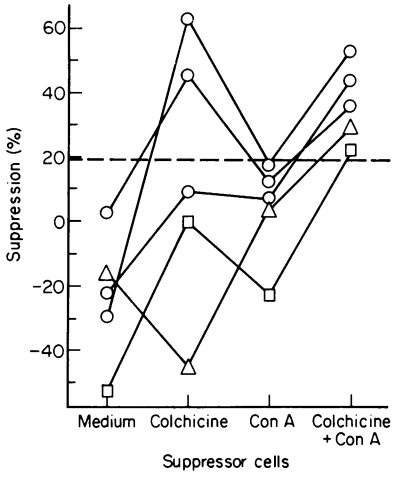

Fig. 3. Effect of *in vitro* colchicine on suppressor cells from *in vivo* untreated FMF patients. Suppressor cells from the proband's second son and the proband's father were cultured in medium, colchicine, Con A, or colchicine plus Con A for 40–44 hr and then cocultured with freshly drawn healthy volunteers' PHA stimulated responder cells. The proband's second son was tested three times between FMF attacks before starting colchicine treatment (○) and once after temporarily discontinuing colchicine treatment (△). The proband's father was tested once after temporarily discontinuing colchicine treatment (squares). The lower limit of normal (mean −2 standard deviations) for healthy volunteers' Con A activated suppressor cell function (19%) is shown by the horizontal dotted line.

The proband's second son's suppressor cells were tested with *in vitro* colchicine three times before he started oral colchicine treatment and once after discontinuing oral colchicine treatment. The proband's father's suppressor cells were tested with *in vitro* colchicine once after stopping oral colchicine treatment. Incubating these *in vivo* untreated FMF patients' suppressor cells with Con A plus 10^{-5} M colchicine significantly ($P<0{\cdot}01$) increased their Con A activated suppressor cell function ($36\pm5\%$) as compared to their Con A activated suppressor cells not incubated with colchicine ($4\pm7\%$) (Table 1, Expt. No. 1; Fig. 3). Thus their suppressor cell deficiency could be corrected by either *in vitro* or *in vivo* colchicine treatment.

The effect of *in vitro* colchicine (without Con A) on these *in vivo* untreated FMF patients' suppressor cells was variable ($14\pm19\%$ suppression as compared to $25\pm8\%$ enhancement by the suppressor cells incubated in medium, $P<0{\cdot}1$). In four out of five assays, their suppressor cells incubated with colchicine suppressed as compared to suppressor cells incubated with medium (Fig. 3). However, their suppressor cells incubated with colchicine only suppressed in two of the five assays when compared to responder cells cultured alone (without putative suppressor cells). When the father and second son were treated with oral colchicine, incubation of their suppressor cells with Con A plus colchicine did not further augment their Con A activated suppressor cell function (Table 1, Expt. No. 2).

DISCUSSION

We found that oral colchicine treatment corrected the FMF patients' suppressor cell deficiency within 1 week of starting treatment. The two adult FMF patients had significantly less (but still normal levels of) Con A activated suppressor cell function when their dose of colchicine was reduced from 2 mg/day to 1 mg/day for 1 month. During this time, they continued to be clinically asymptomatic. Therefore, the change in their suppressor cell function appears to be directly due to the change in their dose of colchicine rather than via a change in the frequency of FMF attacks. The proband's first son with FMF had normal levels of suppressor cell function on 1 mg/day of colchicine even though he still had some FMF attacks. Suppressor cells from two *in vivo* untreated

FMF patients incubated with Con A plus colchicine gave normal levels of suppressor cell function. Furthermore, these *in vivo* untreated FMF patients' suppressor cells incubated with colchicine (without Con A) often suppressed as compared with their suppressor cells incubated with medium. Thus colchicine appears to directly correct the FMF patients' suppressor cell deficiency rather than preventing FMF attacks by unknown mechanisms which then only indirectly results in a correction of the suppressor cell deficiency.

The functional measurement of suppression represents the ratio of helper cell activity to suppressor cell activity. Therefore, our observations of colchicine correcting these FMF patients' Con A activated suppressor cell function could be due to colchicine augmenting suppressor cell activity and/or decreasing helper cell activity.

Oral colchicine treatment of the proband's brother with FMF switched his PHA stimulated responder cells from being non-suppressible to being suppressible by Con A activated suppressor cells from healthy volunteers (Ilfeld *et al.*, 1982b). This suggests that colchicine treatment has multiple effects on immunoregulatory cells.

The question arises as to the mechanisms of action whereby colchicine can modulate suppressor cell function. T lymphocytes stimulated with Con A undergo capping (Loor, 1974), lose Fc-IgM receptors and gain Fc-IgG receptors (Gupta, Schwartz & Good, 1979). When T lymphocytes are incubated with IgG immune complexes, *in vitro* colchicine inhibits capping of the Fc-IgG receptors, inhibits the loss of Fc-IgG receptors, and inhibits the subsequent increase in Fc-IgM receptors (Reaman *et al.*, 1980). This raises the possibility that colchicine might modulate the induction of Con A activated lymphocytes by influencing the expression of cell surface receptors.

In vitro incubation of the *in vivo* untreated FMF patients' suppressor cells with colchicine (without Con A) often induced suppression as compared to no suppressor cells or suppressor cells cultured alone in medium.

This suggests that colchicine can sometimes increase suppressor cell function via a mechanism which is independent of Con A stimulation. The most likely explanation is colchicine's effect on cyclic AMP and/or prostaglandin E.

Colchicine has no effect on lymphocyte cyclic AMP levels when cultured alone without hormones; however, with the addition of isobutylmethylxanthine (a phosphodiesterase inhibitor) (with or without isoproterenol [a β adrenergic agonist] or prostaglandin E_1 [PGE_1]), colchicine markedly potentiated lymphocyte cyclic AMP levels (Rudolph, Greengard & Malawista, 1977).

Macrophages, but not lymphocytes, synthesize and release PGE when treated *in vitro* with colchicine (Gemsa *et al.*, 1980). Con A, colchicine or Con A together with colchicine did not affect cyclic AMP levels in macrophages; however, Con A, colchicine, or Con A together with colchicine markedly enhanced macrophage cyclic AMP production induced by PGE_1 (Gemsa *et al.*, 1977). Furthermore, PGE_1 can induce suppressor T cells (Fulton & Levy, 1981).

After stimulation with PGE_2 plus theophylline, human T cell subpopulations which are Fc-IgG receptor positive (T_G), theophylline sensitive (concerning rosetting with sheep erythrocytes), or H2 receptor positive show greatly enhanced cyclic AMP levels (Raupp *et al.*, 1981). These subpopulations usually (but not always) function as suppressor rather than helper cells (Shore, Dosch & Gelfand, 1978). IgG immune complexes preferentially increase cyclic AMP in T_G cells (Raupp *et al.*, 1981) and activate suppressor cell function of T_G cells. This may explain how *in vitro* and *in vivo* colchicine corrected the FMF patients' suppressor cell deficiency. Whether *in vivo* colchicine corrected the suppressor cell deficiency in a similar or different way as *in vitro* colchicine is not known. We hypothesize that colchicine, acting via a prostaglandin dependent or independent pathway, preferentially increased intracellular cyclic AMP in certain subpopulations of these FMF patients' cells resulting in augmented suppressor cell function and/or decreased helper cell function.

Suppressor cells from patients with asthma (who had decreased Con A activated suppressor cell function) incubated either with isoproterenol or with theophylline (without Con A) subsequently suppressed mitogen stimulated proliferation of untreated autologous cells in coculture (Rola-Pleszczynski & Blanchard, 1981). Also, suppressor cells from three patients with congenital agammaglobulinemia (who had excessive suppressor cell function of their unstimulated cells) incubated either with isoproterenol or with theophylline (without Con A) exhibited significant augmentation of suppressor cell function in co-culture with untreated allogeneic plaque forming

cells (Gelfand *et al.*, 1979). This demonstrates that *in vitro* drugs which increase cyclic AMP can functionally activate patient's suppressor cells.

Our observations with *in vitro* and *in vivo* colchicine treatment of these FMF patients from this particular family suggest that colchicine can assist in activating suppressor cells and/or inhibiting helper cells which can directly correct their Con A activated suppressor cell function. Further studies are needed to determine whether there is normal or abnormal suppressor cell function in FMF patients from other families. Our results raise the possibility that colchicine may be potentially useful in treating patients with other diseases associated with decreased suppressor cell activity or associated with excessive helper cell activity. It is interesting to note that in uncontrolled studies colchicine has been reported to be of therapeutic benefit in treating patients with psoriasis (Wahba & Cohen, 1980), a disease associated with a deficiency of Con A activated suppressor cell function (Sauder *et al.*, 1980), and in treating patients with scleroderma (Alarcon-Segovia, 1979), a disease associated with excessive helper cell function (Krakauer *et al.*, 1981; Mayes *et al.*, 1982). Colchicine has also been reported to be of therapeutic benefit in treating patients with post-hepatitic cirrhosis or alcoholic cirrhosis (Kershenobich *et al.*, 1979). Patients with chronic active hepatitis (Hodgson, Wands & Isselbacher, 1978) and cirrhotic patients with active alcoholic liver disease (Kawanishi *et al.*, 1981) have a deficiency of Con A activated suppressor cell function. Whether the reported clinical effect of colchicine in psoriasis, scleroderma and cirrhosis is due to modulation of immunoregulatory cells and/or other factors is unknown. Further studies are needed to determine the effect of colchicine on helper T cells, suppressor T cells, and monocytes as well as to test colchicine's therapeutic efficacy in diseases associated with decreased suppressor cell activity or excessive helper cell activity.

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