IVERMECTIN-FACILITATED IMMUNITY IN ONCHOCERCIASIS : ACTIVATION OF PARASITE-SPECIFIC TH1 TYPE RESPONSES WITH SUBCLINICAL *ONCHOCERCA VOLVULUS* INFECTION

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The severity of chronic disease produced by the parasitic nematode *Onchocerca volvulus* varies widely, ranging from asymptomatic infection to cutaneous involvement to, most severely, opthalmologic pathology which may finally cause blindness (WHO, 1987). Humans chronically infected with *O. volvulus* not only demonstrate a prominent production of all subclasses of parasite-specific immunoglobulins (Karam and Weiss 1985 ; Dafa'alla *et al.*, 1992), but also a depressed cellular reactivity *in vitro* and a deficient production of IL-2 in response to *O. volvulus*-specific antigenic (OvAg) stimulation (Greene *et al.*, 1983 ; Gallin *et al.*, 1988 ; Ward *et al.*, 1988).

Recent reports suggest that ivermectin, the drug of choice for treatment of onchocerciasis, temporarily eliminates microfilariae (mf) from the skin and also facilitates cellular immunity in treated patients (Steel *et al.*, 1991 ; Freedman *et al.*, 1991 ; Soboslay *et al.*, 1992). Delayed type hypersensitivity (DTH) reactions and circulating lymphocyte subpopulations normalized after a single dose of ivermectin, leading to improved *in vitro* cellular reactivity to mitogenic stimulation and to augmented cellular production of several cytokines by PBMC (Soboslay *et al.*, 1992). These changes appeared rather gradually, and ivermectin-facilitated immune responses controlling microfilaridermia in infected individuals may only reach critical importance after several treatments with ivermectin.

In the present study we have examined the quantitative and qualitative changes registered in the parasite-specific antibody response, cellular reactivity and cytokine production profile in onchocerciasis patients repeatedly treated with ivermectin over a period of 7 years. Our results suggest that parasite-specific cellular immunity of onchocerciasis patients underwent further substantial alterations following repeated treatment ; and therefore therapy may be expected to synergistically contribute to effective control of microfilaridermia in already infected individuals and to increase resistance to re-infection.

The density of *O. volvulus* microfilariae (mf) in treated patients remained significantly reduced, whereas the number of amicrofilaremic patients (subclinical infection) increased with repeated treatments. *In vitro* cellular responses to *O. volvulus* antigen (OvAg) were highest ($p < 0.01$) in untreated control individuals exposed to infection but negative for mf (endemic normals). Cellular reactivity in repeatedly treated patients was higher at 84 than at 36 months post initial treatment (p.i.t.) ; furthermore, the proliferative responses to OvAg, mycobacterial PPD and streptococcal SL-O were greater ($p < 0.05$) at 84 months p.i.t. in amicrofilaremic than in microfilaria-positive onchocerciasis patients. In amicrofilaremic patients such reactivity approached the magnitude observed in endemic normals.

Peripheral blood mononuclear cells (PBMC) from patients and endemic normals produced equivalent amounts of IL-2, IL-4 and IFN-gamma in response to mitogenic stimulation with PHA ; in response to OvAg, however, significantly more IL-2 and IFN-gamma were produced by PBMC from amicrofilaremic patients or endemic normals than by microfilaria-positive patients. OvAg-specific production of IL-4 by PBMC from treated patients was lower at 84 than at 36 months p.i.t.

At three months p.i.t. the titers of circulating OvAg-specific IgG_{1-3} had increased ($p < 0.05$), but they then continuously declined with repeated treatments. Only IgG_1 and IgG_4 bound to OvAg of Mr 2-12k at 1 month p.i.t., while recognition of OvAg of Mr 10-200k by IgG_1, IgG_2 and IgG_4 reached a maximum intensity at 3-6 months p.i.t., with the overall intensity of binding to OvAg gradually weakening thereafter.

These results suggest that onchocerciasis-associated immunosuppression is reversible following invermectin-induced permanent clearance of microfilariae from the skin ; and that a vigorous parasite-specific cellular reactivity and a sustained production of IL-2 and IFN-gamma in amicrofilaremic individuals may contribute to controlling *O. volvulus* infection.

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