Differential Decline in Filaria-Specific IgG1, IgG4, and IgE Antibodies in *Brugia malayi*–Infected Patients after Diethylcarbamazine Chemotherapy

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In human filariasis, the predominant serum antibody is IgG4, accompanied by significant IgE production. The ratio of IgG4 to IgE is highest in asymptomatic microfilaremic carriers, while chronic disease is associated with elevated IgG1–3. The changes in isotypes following chemotherapy with diethylcarbamazine (DEC) were studied in 2 groups of *Brugia malayi*–infected patients from Sumatra and South Kalimantan, Indonesia. Similar results were obtained from each group. IgG4 levels decreased sharply (65%–78%) within 12 months. IgG1 levels declined in a less consistent and extreme manner, and levels of IgG2 and IgG3 declined only in patients with elephantiasis, who also had the highest initial levels of these antibodies. IgE responses were relatively stable to therapy in microfilaremic patients (7%–28% reduction) and showed only moderate decline (56% over 2 years) in elephantiasis patients. Active filarial infection is thus associated with specific IgG4 antibodies, but there is independent expression of the IgE and IgG4 isotypes in filariasis.

Human infection with filarial nematode parasites induces unusually high levels of specific IgG4 and IgE antibodies [1, 2]. The magnitude of filaria-specific IgG4 responses in microfilaremic patients (geometric mean concentration, 762 μg/mL) [2] is such that it often exceeds the total IgG4 concentration in serum of uninfected subjects, which is typically 240 μg/mL [3]. The amplitude and uniformity of the IgG4 antibody response has led to the suggestion that high titers of this isotype are diagnostic of both lymphatic filarial infestation [4] and infection with *Onchocerca volvulus* [5]. One interpretation of these findings is that filarial parasites may selectively drive class switching in this direction, either directly or through activation of Th2 helper cells.

Diethylcarbamazine (DEC), an effective drug for the treatment of lymphatic filariasis, rapidly clears circulating microfilariae (Mf) and, with prolonged treatment, kills adult parasites [6–8]. DEC therapy offers an opportunity to observe changes in the isotype balance in patients after microfilarial clearance and to test the hypothesis that active infection drives the dominant IgG4 response. It is also of interest to compare IgG4 and IgE dynamics, as these isotypes are differentially regulated in lymphatic filariasis [2] even though both are known to be promoted by the Th2-derived cytokine, interleukin-4.

The balance of specific isotypes is also of central importance to the natural history of filarial infection. IgE and IgG4 antibodies in individual patients display similar recognition specificities [9], so that high levels of IgG4 are likely to functionally block IgE-mediated reactions in vivo [10]. However, whether such blocking antibodies protect the parasite from elimination or the host from immunopathology remains to be determined. In addition to high levels of IgG4, other intriguing patterns of isotype expression have been noted in microfilaremic patients: Cases of advanced disease and chronic pathology are associated with higher IgG1 and, in particular, IgG2 and IgG3 isotypes [2, 11, 12]. Thus, the use of particular isotypes in the antifilarial response may have a major influence on the outcome of infection.

There is also an epidemiologic dimension to the study of filarial antibody responses. Poorly sensitive night blood–smear tests must be replaced by a simple serologic marker for lymphatic filarial infection. Quantitation of antifilarial IgG4 has been suggested as a diagnostic tool with improved specificity [13]. In addition, the assessment of community-based disease management strategies, such as mass chemotherapy and vector control, would be enhanced if there were known molecular markers (antibody types or specificities) that decline with the removal of parasite infection or transmission, as has recently been suggested in onchocerciasis [14]. The purpose of this study was to compare changes in isotypes in clinically distinct *Brugia malayi*-infected patients before and after treatment with DEC.

Materials and Methods

Study populations. Unrelated patient groups in two areas in which *Brugia* filariasis is endemic were studied. The first group,

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Informed consent was obtained from all patients before clinical and parasitologic study and before blood was obtained in accordance with the guidelines of Indonesia Department of Health and Human Services.

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from Rengat, Sumatra, in Indonesia, comprised 75 subjects who were compared before and 1 year after beginning chemotherapy with DEC and 21 subjects who were in the second year after treatment. In the first year after treatment, 15 subjects were considered normal (endemic normals), 24 were microfilaremic, and 36 had chronic filariasis. Blood microfilaremia was detected by blood smear or, in some cases, by filtration (Nuclepore, Pleasanton, CA) of a 1-mL nighttime sample of venous blood. Because cryptic infection of asymptomatic persons is common in filaria-endemic areas, DEC administration is advisable for all residents, including those in the endemic normal category. All 21 second-year patients were from the chronic filariasis group. DEC (100 mg/week) was administered for up to 2.5 years, with an annual boost of 3 × 100 mg for 10 consecutive days [15].

The second group, from South Kalimantan, Indonesia, comprised 62 microfilaremic patients with *B. malayi* infection. Blood microfilaremia was estimated by filtration (Nuclepore) of a 1-mL nighttime sample of venous blood on two occasions 3 months apart. The mean of the two counts was used as the pretreatment level of microfilaremia. On the second occasion, serum samples were also recovered and stored at −70°C. DEC was then given according to standard protocols, and serum samples were collected again 8 months after treatment. The paired sera from each subject before and after treatment were subsequently tested for antifilarial IgG1, IgG4, and IgE.

IgG isotype ELISA. Standard ELISA protocols were used as described previously [2]. In brief, *B. malayi* adult somatic extract antigen (BmA) was coated onto ELISA plates at 1 μg/mL in 0.06 *M* carbonate buffer, pH 9.6, and the plates were incubated overnight at 4°C. Wells were blocked with 5% fetal calf serum in TRIS-buffered saline, pH 8.5, and incubated with test sera diluted 1/200. A standard curve of high-titer serum with a known concentration of filaria-specific antibodies was included for each isotype in each experiment over a range of dilutions (1/100–1/12800). After a 2-h incubation at 37°C, wells were washed and treated with monoclonal anti-isotype antibodies (mouse anti-human IgG1, M15015; anti-IgG2, M10015; anti-IgG3, M74011; and anti-IgG4, M11013 [all from Oxoid, Basingstoke, UK]) at working dilutions of 1/2000, 1/1000, 1/500, and 1/2000, respectively. After 1 h at 37°C, plates were washed, and peroxidase-conjugated anti-mouse immunoglobulin (P-260; Dako, High Wycombe, UK) was added for 30 min. Last, ABTS substrate (Kirkegaard & Perry, Gaithersburg, MD) was added, and plates were read at 405 nm after 10–20 min. All test optical density measurements were converted to micrograms per milliliter by reference to appropriate standard curves.

IgE ELISA. An ELISA was used to determine specific antifilarial IgE levels. To preclude interference by serum IgG with this assay, all sera were first adsorbed onto protein G Sepharose fast-flow beads (Pharmacia, Milton Keynes, UK) by mixing 30 μL of washed beads with 10 μL of serum overnight at 4°C on a rotator. The adsorbed serum was recovered by brief microcentrifugation and diluted for addition to ELISA plates, taking account of the 4-fold dilution incurred by adsorption.

ELISA plates were coated, as described above, with BmA (5 μg/mL) overnight in carbonate buffer at 4°C. Coated plates were blocked, washed, and incubated with test sera diluted 1/800 or with serial dilutions of a standard serum of known antifilarial IgE concentration for calibration of a standard curve. Plates were incubated overnight at room temperature and then washed and incubated with biotinylated anti-IgE (vector BA 3040) at 1/1000. After 4 h at 37°C, plates were again washed and peroxidase-conjugated streptavidin (P-397, Dako) diluted 1/3000 was added for 1 h at 37°C. After a final wash, trimethylbenzidine substrate was added as described [16], the reaction was stopped with 2 *M* H2SO4, and optical densities were read at 450 nm.

Statistical analysis. Changes in each isotype of specific antifilarial antibody were analyzed for statistical significance using the paired *t* test with Statistica 1.7 (StatSoft, Tulsa, OK) software for Apple Macintosh computers.

Results

Two groups of patients from filaria-endemic areas of Indonesia were studied by comparing antifilarial antibody levels before and after DEC chemotherapy. In a cross-sectional study, patients selected from Rengat represented each of the major categories found in areas of filarial transmission: endemic normal, microfilaremic, and chronically infected. In the second study, involving only microfilaremic patients from South Kalimantan, the levels of Mf were enumerated at each time point.

IgG isotypes after DEC treatment in a cross-sectional study. A total of 75 persons were compared before and 1 year after beginning long-term, low-dose DEC therapy; almost half were elephantiasis patients. Levels of all four IgG isotypes and of serum IgE antibodies were measured by reaction to BmA. During this 1-year study period, specific IgG1 antibodies decreased by ~50% in the microfilaremic and elephantiasis subjects but changed little in the endemic normal group (table 1). IgG2 and IgG3 antibody titers did not show consistent alterations; however, IgG4 antibody titers decreased dramatically in microfilaremic (66% reduction) and elephantiasis (65% reduction of a lower mean titer) patients (table 1). Moreover, this loss was particularly dramatic in persons with very high initial IgG4 concentrations (figure 1, center). These changes in IgG1 and IgG4 were significant for both groups ($P < .005$, paired *t* test).

In the endemic normal subjects, there was a slight increase in the level of IgG1, and the mean level of IgG4 declined by 46%, although the difference was not significant ($P = .057$). Our interpretation of the elevation in IgG4 and the subsequent reduction in IgG4 in these asymptomatic, amicrofilaremic persons after DEC treatment is that many of them harbor cryptic *B. malayi* infections that are not detected by blood filtration tests [2].

IgE antibodies after DEC treatment. In the same patient set, IgE levels after 1 year of DEC treatment showed relatively little change, despite the marked changes in levels of IgG1 and IgG4 (table 1). Thus, in elephantiasis patients (who had the highest levels of filaria-specific IgE), IgE titers declined by only 21%, while titers in microfilaremics declined <10% ($P = .40$). However, as with IgG4, the largest reductions in IgE were seen in subjects with the highest initial levels of specific IgE antibody (figure 1).

Antibody levels after 2 years of treatment. A subset of the study cohort (21 elephantiasis cases) also made themselves

Table 1. Filaria-specific IgG and IgE levels in 3 groups of subjects before and after treatment with DEC.

Isotype	Endemic normal (n = 15)	Microfilaremic* (n = 24)	Elephantiasis (n = 36)
IgG1			
Before treatment	19.3	72.8	130.7
After treatment	24.9	37.3	64.5
% reduction†	−29.0	48.8	50.7‡
IgG2			
Before treatment	26.9	20.5	56.1
After treatment	25.8	31.8	39.3
% reduction†	4.1	−55.1§	29.9‖
IgG3			
Before treatment	20.9	20.1	24.0
After treatment	22.2	20.1	17.8
% reduction†	−6.2	0.0	25.8
IgG4			
Before treatment	79.4	451.5	199.4
After treatment	43.0	154.2	69.3
% reduction†	45.8	65.8¶	65.2**
IgE			
Before treatment	9.6	19.5	32.3
After treatment	6.5	18.0	25.5
% reduction†	32.3††	7.7	21.1‡‡

NOTE. Data are geometric means in μg/mL (IgG) or ng/mL (IgE) of filaria-specific antibody.

* Includes 6 subjects who did not clear microfilariae after treatment; exclusion of these subjects does not significantly change % reduction for each isotype (IgG1, 50.8%; IgG2, −63.9%; IgG3, −1.0%; IgG4, 76.0%; IgE, 5.8%).

† Calculated as [(before treatment) − (after treatment)] × 100/(before treatment). Negative values represent % increase. Statistically significant comparisons: ‡P = .015; §P = .010; ‖P = .031; ¶P = .005; **P < .001; ††P = .036; and ‡‡P < .024.

available for a 2-year follow-up. In this subset, changes in IgG isotypes in the first year were slightly more profound than those in the group as a whole, and by the second year, more substantial reductions were evident (figure 1). Thus, IgG4 levels were 17.5% of the initial values, and all other isotypes were reduced by 45%–68%. Of interest, 3 of the elephantiasis patients were positive by blood filtration for Mf at the end of the second year. Whether or not this indicates resistance to DEC [17], it is notable that these subjects were among those in the whole group with the highest residual IgG4 levels (figure 1, ○), although their IgG1 and IgE antibodies were not relatively high.

IgG isotypes in microfilaremic subjects after DEC treatment. The 62 microfilaremic subjects from South Kalimantan showed substantial heterogeneity in response to DEC. We therefore divided the study population into 3 groups, according to the extent of Mf clearance. Group A (44% of the population) comprised those who responded by completely clearing blood parasites; group B (16%) comprised those who showed dramatic but incomplete reduction (to <1% of the pretreatment count) in Mf; group C (40%) showed only partial loss of Mf (table 2). Group C had higher initial Mf counts, lower initial titers of IgG1 and IgG4, and were marginally younger than those in the other groups. All patients were serologically characterized before and 8 months after therapy.

Complete or almost complete (>99%) clearance of Mf (groups A and B) resulted in substantial reductions in IgG4 antibody titers, with only 22% of the original level being present 8 months after therapy (table 2). These subjects also showed >50% loss of IgG1, but of interest, their IgE levels declined only slightly (27%–29%). In contrast, group C, which had only partial clearance of Mf, remained at >50% of the original level of IgG4 and at ~75% of the initial levels of IgE and IgG1. Changes in IgG1 were more gradual: Group A declined to 33%, B to 46%, and C to 72% of the original titer. Overall, IgE responses were much less influenced by chemotherapy and showed little difference according to the degree of Mf clearance (figure 2).

Correlations with microfilarial density. Several earlier studies reported significant correlations between pre- or post-treatment intensities of microfilaremia and immunologic variables, such as IgG4 [4, 18]. We subjected our data set to a full range of correlative analyses but found no statistically

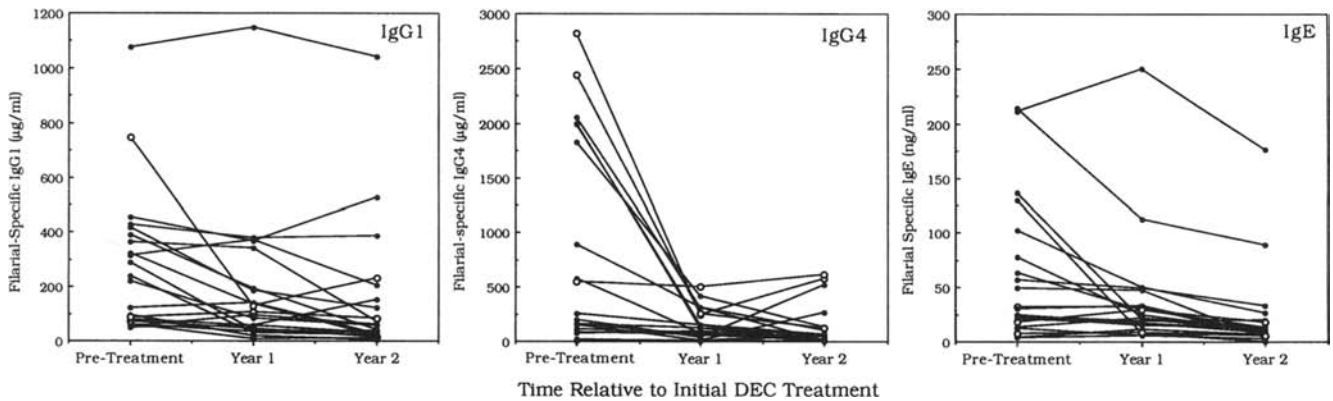

Figure 1. Changes in filaria-specific IgG1, IgG4, and IgE responses to *B. malayi* adult worm extract in 21 Sumatran elephantiasis patients, from before to 1 and 2 years after beginning DEC treatment. ○, 3 patients who were microfilarial positive at final survey. Each serum sample was measured by ELISA, and antibody concentrations were calculated with reference to standard curve, enabling linear comparisons.

Table 2. IgG1, IgG4, and IgE responses in microfilaremic patients before and after treatment with DEC.

	Group A (n = 27)	Group B (n = 10)	Group C (n = 25)	All groups (n = 52)
Age (years, mean)	50.6	45.0	40.8	45.4
Microfilariae				
Before treatment	337.0	360.6	526.7	408.1
After treatment	0.0	2.0	80.0	27.3
% reduction	100.0	99.4	84.8	93.3
IgG1				
Before treatment	61.1	76.6	47.0	57.0
After treatment	20.0	35.0	33.7	27.0
% reduction	67.3	54.4	28.3	52.7
IgG4				
Before treatment	605.5	604.2	367.6	495.0
After treatment	131.8	128.3	204.1	156.6
% reduction	78.2	78.8	44.5	68.4
IgE				
Before treatment	52.5	98.4	58.3	60.6
After treatment	37.4	72.0	43.6	44.2
% reduction	28.8	26.8	24.2	27.1

NOTE. Clearance was complete in group A, incomplete in B, and partial in C. Data (except age) are geometric means. % reduction represents change in geometric means. Posttreatment sera were taken 8 months after DEC therapy. IgG isotypes are μg/mL specific antifilarial antibody; IgE data are ng/mL.

significant correlation between any combination of age, IgE, IgG1, and IgG4 levels, percent reduction in these levels, and either pretreatment counts of Mf or percent decrease in Mf. Most important, no association was apparent between density of Mf and IgG4 titer (figure 3A). This result is relatively robust, as the Mf density for the South Kalimantan patients was determined on two occasions. However, when the degree of reduction in IgG4 is charted against the density of Mf after treatment,

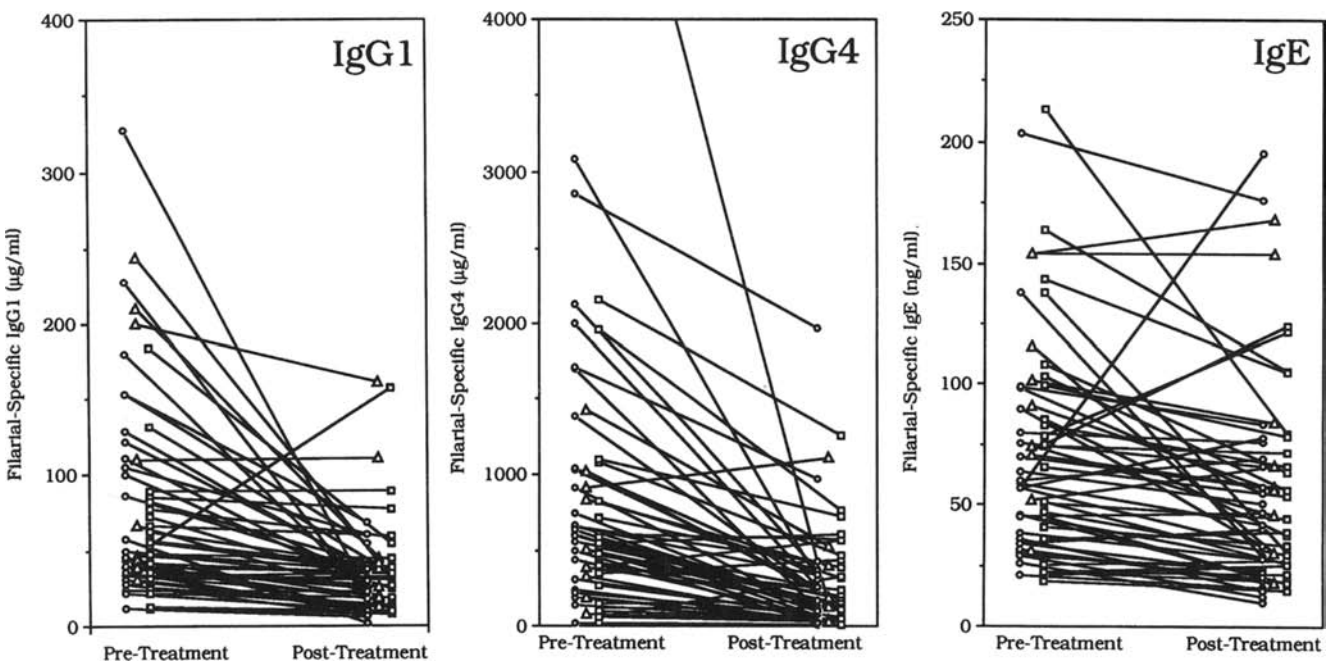

Figure 2. Changes in filaria-specific IgG1, IgG4, and IgE responses to *B. malayi* adult worm extract in 62 microfilaremic patients from South Kalimantan, who in response to DEC therapy, showed complete clearance (○), incomplete clearance (△), or partial or no clearance (□).

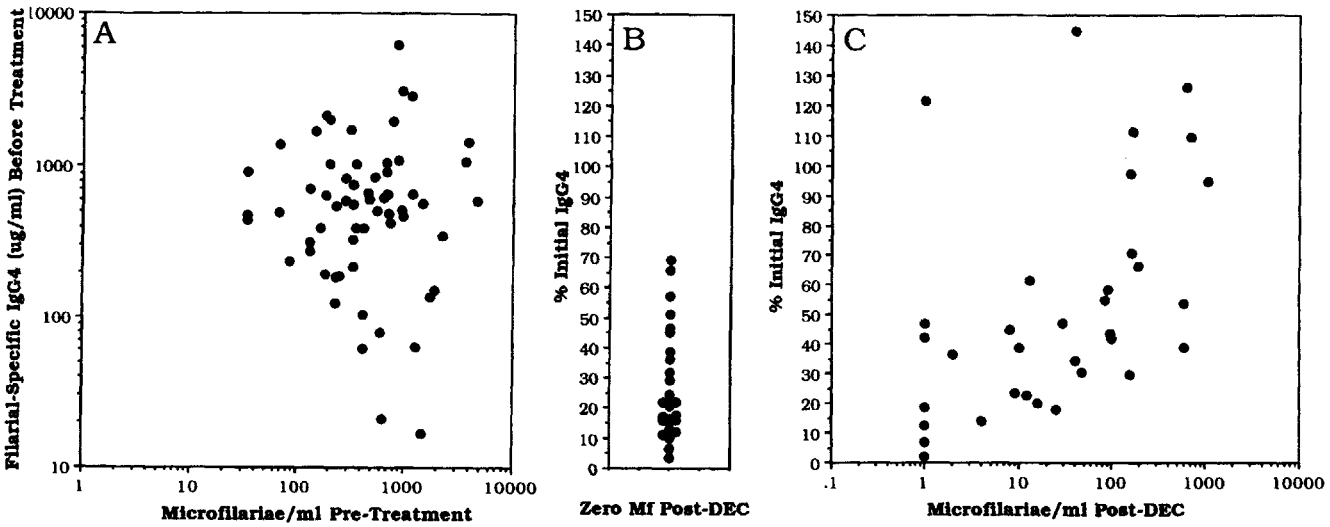

Figure 3. Correlations between microfilarial densities and IgG4 responses in South Kalimantan study of 62 microfilaremic subjects. **A**, Lack of correlation between initial IgG4 serum antibody levels and the microfilarial density in same person. **B**, **C**, Changes in IgG4 levels, relative to initial concentration as 100%, plotted against residual microfilarial intensity. **B**, Subjects who cleared microfilariae (Mf); **C**, subjects with residual parasites at end of 8 months.

as previously described [18], a clear trend was apparent, which supports the previously reported finding that IgG4 declines in inverse proportion to the residual microfilarial density (figure 3B, C).

Discussion

DEC is a rapid microfilaricide that can also kill adult *B. malayi* and *Wuchereria bancrofti* worms over a longer time period, particularly with repeated doses [6, 19, 20]. Filarial parasites are thought to induce major perturbations to the host immune system [21–23], and the comparison of filariasis patients before and after DEC therapy may, therefore, be instructive if clearance of parasites is accompanied by reversal of immune modulation. For example, it is well established that microfilaremic patients show antigen-specific unresponsiveness in proliferation of peripheral T lymphocytes [24–27]. Most significant, DEC treatment restores this immune response in treated persons [28–30].

On the humoral level, one of the major distortions achieved by filarial parasites is the remarkable amplification of specific IgG4 antibodies [1, 2, 4, 5]. In some studies, a correlation is evident between microfilarial density and IgG4 levels [4] and between posttreatment microfilaremia and residual IgG4 titers [18]. Thus, the microfilarial stage has been the prime candidate for a parasite-driven factor that drives IgG4 expression.

Our results show that IgG4 is the antibody isotype most sensitive to the effects of antifilarial chemotherapy, a finding consistent with the hypothesis that this subclass is selectively amplified by filarial parasitism. In both study groups, DEC produced a ≥65% reduction in IgG4; levels of other IgG isotypes and IgE changed less or insignificantly. It may be significant that similar reductions were observed in both microfilaremic patients and patients with chronic pathology. If Mf were driving the IgG4 amplification, the effect of DEC treatment would be apparent only in the patent microfilaremic cases rather than, as we observed, in all patients irrespective of initial Mf density. Moreover, our finding that incomplete clearance produces a decline in IgG4 titers as great as that seen in complete elimination of Mf argues that the microfilarial stage may indeed not be responsible for stimulation of this isotype. Conversely, IgG4 levels decline more severely in DEC-treated patients than in those treated with ivermectin, which clears Mf without macrofilaricidal effect [18]. Thus, the adult worm, resident in the lymphatics, is the most likely source of the IgG4 potentiation. Experiments in a murine model support this latter contention, because it is adult worms and not Mf that stimulate a potent Th2 helper cell response and consequent interleukin-4 production [31].

It is widely thought that IgG4 acts as a blocking antibody to prevent IgE-mediated hypersensitivity reactions [10], presumably due to the shared specificity of IgG4 and IgE in any individual [9]. Our previous data could be construed in favor of this hypothesis in that patients with chronic filarial disease had a high level of IgE, as well as IgG1, -2, and -3, and low IgG4, while asymptomatic microfilaremics exhibited extraordinarily high IgG4 and a reduced IgE concentration [2]. The fact that levels of IgE decline more slowly than do levels of IgG4 means that one effect of treatment is the reduction of the IgG4:IgE ratio, which in turn lowers the potential for IgG4 to block IgE-mediated hypersensitivity reactions. Since DEC treatment is associated with resolution rather than exacerbation of disease [7], this outcome implies that clinical filariasis does not depend on IgE-mediated immunopathologic reactions.

IgG4 antibody responses in filariasis are instructive markers of infection, even when, as described here, they are measured against a complex mixture of parasite antigens. Responses to individual filarial antigens may be particularly valuable for both diagnosis and analysis of the course of infection. Thus, a recombinant protein from *B. malayi*, SXP-1, is the target of an IgG4-restricted response in natural infection, and levels of these antibodies decline sharply after DEC therapy [32]. Together these results pave the way for identifying molecular markers that will define active infection in human lymphatic filariasis. Such markers could be advantageously used to generate new diagnostic tests for individual infection and community parasite load [33].

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HIV-1 MDR: Virus HIV-1 multiresistente; PLHIV: Persone che vivono con l'HIV.

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Regime di dispensazione: medicinale soggetto a prescrizione medica limitativa, da rinnovare volta per volta, vendibile al pubblico su prescrizione di centri ospedalieri o di specialisti - infettivologo (RNRL).

La segnalazione delle reazioni avverse sospette che si verificano dopo l'autorizzazione del medicinale è importante, in quanto permette un monitoraggio continuo del rapporto beneficio/rischio del medicinale.

Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta tramite il sito web dell'Agenzia Italiana del Farmaco:
https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse

▼Medicinale sottoposto a monitoraggio addizionale. Ciò permetterà la rapida identificazione di nuove informazioni sulla sicurezza. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta.

1. Rukobia Riassunto delle Caratteristiche del Prodotto
RCP RUKOBIA

ViiV Healthcare

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