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Review: Leishmaniasis in the United States: Treatment in 2012

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Abstract. Although civilian physicians in the United States seldom encounter patients with leishmaniasis, therapeutic advances in endemic regions have opened the door to approaches that can be applied in this country. Advances revolve around the use of oral miltefosine in all forms of leishmaniasis and the use of short-course intravenous liposomal amphotericin B in visceral and possibly cutaneous infection. Lengthy, traditional intravenous treatment with pentavalent antimony (sodium stibogluconate) still has a role in the United States; however, although expensive, miltefosine and liposomal amphotericin B are considerably more appealing selections for initial therapy.

INTRODUCTION

Leishmaniasis, an intracellular protozoal infection in which tissue macrophages are targeted, is transmitted by sandfly bite and occurs in 98 countries. Fully expressed infection, caused by a diverse group of species, results in three basic clinical diseases—cutaneous (CL), mucosal (ML), or visceral (VL) leishmaniasis. Ten countries (Afghanistan, Iran, Iraq, Saudi Arabia, Algeria, Ethiopia, Sudan, Syria, Brazil, and Peru) contain > 90% of cases of CL, six countries (India, Bangladesh, Nepal, Sudan, Ethiopia, and Brazil) house > 90% of the world's VL burden, and ML is primarily but not exclusively a disease of South America.[1,2]

When civilian physicians in the United States are called on to manage patients with leishmaniasis, which is not often, it is usually in a predictable setting (Table 1), most commonly travelers with localized CL. After the diagnosis has been secured,[2–5] it is important to determine the extent of disease, region acquired, and infecting species (if possible), because this information may influence the choice of therapy, particularly in CL.

ML and VL, seldom encountered in the United States, are always treated. Although treatment is not required in CL in all instances, in practice, most patients in the United States receive some type of drug therapy. Irrespective of the treatment, patients with any form of leishmaniasis should be made aware of two possibilities: first, that the initial response may prove unsatisfactory, requiring retreatment, and second, that despite a satisfactory clinical response, relapse may still occur within the first 6–12 post-treatment months.

In endemic regions, multiple antileishmanial agents are in use or have been tested (Table 2). Although treatment efficacy may vary by species and/or region of acquisition, four drugs, known or likely active in all forms of leishmaniasis, are available to or can be obtained by US clinicians and used in both adults and children. Three are administered intravenously (IV; sodium stibogluconate, amphotericin B deoxycholate, and liposomal amphotericin B), and one is administered orally (miltefosine).[2] Other available drugs may be of limited, species-specific use, primarily in New World CL (NWCL)—oral ketoconazole for *Leishmania* (*V.*) *panamensis* or *L.* (*L.*) *mexicana* infection, IV pentamidine for *L.* (*V.*) *guyanensis* infection, and perhaps, oral fluconazole for *L.* (*V.*) *braziliensis* as well as *L. major* infection, the latter being an agent of Old World CL (OWCL).[2,3,5,25] The only US Food and Drug Administration (FDA)-approved agent for any form of leishmaniasis (VL is the indication) is liposomal amphotericin B.[26]

TRADITIONAL ANTILEISHMANIAL TREATMENT IN THE UNITED STATES: PENTAVALENT ANTIMONY

Pentavalent antimony, in the form of sodium stibogluconate (Pentostam; GlaxoSmithKline, Middlesex, UK), represents time-tested, conventional therapy in the United States. Sodium stibogluconate is an investigational new drug (IND) product provided at no charge by the Centers for Disease Control (CDC) under its IND protocol. Drug is administered at 20 mg/kg by a 10- to 15-minute IV infusion one time daily for 10–20 days in CL and 28 days in ML and VL (Table 3).

Although used for > 60 years, the pentavalent antimonials remain active worldwide, with the exception of VL (kala-azar) acquired in northeastern India in the highly endemic Bihar State.[2] Elsewhere, antimony therapy (with retreatment, if necessary) produces cure rates in immunocompetent patients in the range of 70–90% in CL, 60–90% in ML, and > 90% in VL.[2–6] Cure rates vary in a clinically frustrating way in CL and ML by endemic region, infecting species, disease severity, drug dose used, and particularly in VL, host immunocompetence.[1–4]

In 2012 in the United States, sodium stibogluconate is considered a satisfactory agent from the standpoint of efficacy. However, tangible drawbacks have always made antimony therapy unappealing. First, treatment is typically arduous. Frequent adverse clinical and/or biochemical reactions (Table 4) necessitate close monitoring and at least once weekly blood, urine, and electrocardiographic testing during therapy; treatment needs to be interrupted in up to ~25% of patients but can be restarted and often completed. Second, sodium stibogluconate is not FDA-approved; thus, after CDC approval, local institutional review board (IRB) permission is also required. Third, daily IV outpatient administration for up to 20 days or longer may not be easy to accomplish, and an indwelling venous catheter may be needed. Fourth, although sodium stibogluconate is provided by a federal agency (CDC), home antibiotic infusion services may refuse to administer a drug that is not FDA-approved, and health insurance companies may decline its administration costs. Finally, the pentavalent antimonials cannot be used in pregnant women.

Given the preceding drawbacks, it is not surprising that civilian and military physicians are willing to consider reasonable

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TABLE 1
Settings in which US civilian physicians may encounter leishmaniasis[2–17]

Setting	CL	ML	VL
Infection acquired in an endemic region			
Immigrant	+	+	+
Traveler, field worker, or expatriate	+	+	+
Former soldier or military contractor	+		+
Immunocompromised patient*	+	+	+
Infection acquired in the United States†			
Laboratory accident	+		
Sandfly bite (Texas, OK)	+		
Blood product transfusion or needle use			+

Cutaneous leishmaniasis (CL), particularly in travelers, is by far the form encountered in the United States; mucosal (ML) and visceral leishmaniasis (VL) are seen rarely.

* Most likely VL and most often reactivation of quiescent, previously acquired (subclinical or treated) infection provoked by acquired T-cell deficiency (e.g., advanced HIV disease) or iatrogenic immunosuppression by corticosteroid or antitransplant rejection therapy, cancer chemotherapy, or anticytokine treatment (e.g., antitumor necrosis factor therapy).[12–14]

† Irrespective of the laboratory strain accidently injected, if infection develops, it is usually (but not invariably) confined to the skin.[15] CL is occasionally acquired in Texas and Oklahoma.[16] Blood-borne transmission of VL is theoretically possible in the United States.[17]

alternatives to sodium stibogluconate. Fortunately, recent experience derived from endemic regions in all forms of leishmaniasis has opened the door to additional therapeutic options for patients cared for in this country.

TREATMENT USING LIPOSOMAL AMPHOTERICIN B

Conventional amphotericin B deoxycholate, an agent with well-recognized adverse reactions that is typically difficult to tolerate in prolonged regimens (Table 3), is extremely active in VL and has been used as rescue therapy in both CL and ML.[2–4] Because the better-tolerated liposomal formulation is widely available in the United States, there is no reason to use the deoxycholate form to treat leishmaniasis. The only exception might be drug cost—not a minor issue if the patient is responsible for treatment expenses. Liposomal amphotericin B (AmBisome; Gilead Sciences, San Dimas, CA) is expensive; drug cost alone in the FDA-approved regimen for VL (total dose of 21 mg/kg) is $5,000–6,000 for a 70-kg person. Health insurance companies may well balk at this amount (as well as infusion and laboratory monitoring costs) in patients with CL, because this form of leishmaniasis is not an FDA-specified indication.

Liposomal amphotericin B is well-established in endemic regions for the treatment of VL; optimal short-course regimens regularly induce cure rates of ≥ 95%.[2,19,27] Indian VL is most responsive, whereas Brazilian and Sudanese VL seem less responsive.[2,19] Although treatment experience is still quite limited, this agent is also likely active in CL and probably, ML.[9,11,29,30,32,33]

The FDA-approved regimen for liposomal amphotericin B in VL in immunocompetent patients is administered as a total dose of 21 mg/kg in an arbitrarily selected, cumbersome fashion—seven infusions over a lengthy 21-day period (Table 3).[26] Drug is given over 2 hours, and treatment may be preceded by a 1-L saline infusion to reduce potential nephrotoxicity[29] and an oral antipyretic and/or antihistamine to manage infusion-associated fever and/or rigors (Table 4). As with any amphotericin B-containing product, some patients may not tolerate consecutive-day infusions. Although not often encountered with short-course therapy, the possibility of hypokalemia, anemia, or mild renal insufficiency requires one or perhaps, two times per week complete blood counts and monitoring of serum chemistries.[29] Liposomal amphotericin B, an FDA pregnancy category B drug, has been safely used to treat VL in pregnant women.[34]

TREATMENT USING MILTEFOSINE

Miltefosine (Impavido; Paladin Labs, St. Laurent, Quebec, Canada), the only effective oral agent in VL and ML,[2,28] is on the World Health Organization's Essential Medicines List and registered for VL and CL in 13 countries, but it is not FDA-approved. The drug can be obtained by US physicians from the manufacturer through an IND application to the FDA and local IRB approval (Table 2). Health insurance would not likely cover the cost of imported drug, which for 28 days of treatment at 150 mg/day, is approximately $3,000. Miltefosine is contraindicated in pregnant or breastfeeding women, and satisfactory contraception must be used in women of childbearing age during and for 3 months after treatment.

In endemic regions in immunocompetent patients, a 28-day regimen induces cure rates of 60–80% in ML[28] and usually > 90% in VL.[2,20] In NWCL, clinical cure responses range from

TABLE 2
Antileishmanial chemotherapy in 2012[1–5,18–24]

Drug	Available in the United States	In use or tested	Current clinical usefulness
Sodium stibogluconate	Pentostam*	All forms of infection†	All forms of infection
Pentamidine	Pentam and generic	VL, NWCL, and ML	NWCL (*L. guyanensis*)‡
Amphotericin B deoxycholate	Fungizone and generic	VL, NWCL, and ML	VL; likely NWCL and ML
Liposomal amphotericin B	AmBisome	All forms of infection	VL; likely CL and possibly ML
Amphotericin B lipid complex	Abelcet	VL	Likely VL
Amphotericin B cholesteryl dispersion	Amphotec	VL	Likely VL
Paromomycin	Not available§	VL and NWCL	VL (Indian subcontinent and East Africa)
Miltefosine	Impavido*	All forms of infection	VL, NWCL, and ML; likely OWCL
Ketoconazole	Nizoral and generic	VL and NWCL	Likely NWCL (*L. panamensis* and *L. mexicana*)
Fluconazole	Diflucan and generic	OWCL and NWCL	Possibly OWCL and NWCL
Itraconazole	Sporonox and generic	NWCL and OWCL	Little
Paromomycin (topical)	Not available	NWCL and OWCL	Possibly OWCL and NWCL¶

ML = mucosal leishmaniasis; NWCL = New World cutaneous leishmaniasis; OWCL = Old World cutaneous leishmaniasis; VL = visceral leishmaniasis.

* Not approved by the FDA. Sodium stibogluconate is provided by CDC. To inquire about access to miltefosine as an investigational drug and a single-use IND application, contact Dr. Robert Vinson (Paladin Labs, St. Laurent, Canada) at rvinson@paladinlabs.com.

† Commonly responsible strains: VL (*L. donovani*, Indian subcontinent and East Africa; *L. infantum* [*L. chagasi*], South America and Mediterranean basin); NWCL (*L. braziliensis*, *L. panamensis*, *L. guyanensis*, and *L. mexicana*); ML (*L. braziliensis*, *L. panamensis*, and *L. guyanensis*); and OWCL (*L. major* and *L. tropica*).

‡ *L. guyanensis* infection may respond poorly to pentavalent antimony but well to pentamidine; given the latter's toxicity, it is the only indication for this treatment.

§ Paromomycin is effective in VL[21] but is not FDA-approved or available for importation. Although inexpensive, paromomycin has no obvious appeal for US clinicians, because it requires one time daily intramuscular injection for 21 days.

¶ New formulation being tested.[22]

TABLE 3
Representative treatment regimens for immunocompetent patients in the United States.[1–6,19,20,27–30]

Disease and drug	Regimen	Comments/endemic regions
Visceral		
Liposomal amphotericin B	3 mg/kg, days 1–5, 10 and 21	FDA-approved regimen (all regions)
Liposomal amphotericin B	3 mg/kg, days 1–5 and 10	Mediterranean region
Liposomal amphotericin B	10 mg/kg one time or 3 mg/kg, days 1–5	India
Miltefosine*	2.5 mg/kg per day × 28 days*	India (and likely all regions)
Sodium stibogluconate*	20 mg/kg per day × 28 days	All regions except Bihar State, India
Amphotericin B deoxycholate	1 mg/kg × 15 doses given qod or qd	India (likely all regions)
Mucosal		
Miltefosine*	2.5 mg/kg per day × 28 days*	South America
Sodium stibogluconate*	20 mg/kg per day × 28 days	South America
Cutaneous		
Miltefosine*	2.5 mg/kg per day × 28 days*	Region- and strain-specific activity
Sodium stibogluconate*	20 mg/kg per day × 10–20 days†	All regions
Liposomal amphotericin B	3 mg/kg, days 1–5, 10 and 21, 1–5 and 10, or 1–7	Limited experience in CL
Ketoconazole	600 mg per day × 28 days	*L. panamensis* or *L. mexicana* only
Pentamidine	4 mg/kg, days 1 and 3	*L. guyanensis* infection only

* Not FDA-approved. In adults, recommended daily dose of miltefosine is 100 mg for weight < 45 kg and 150 mg for ≥ 45 kg.
† See text for treatment duration.
qd = daily; qod = alternate day.

50% to 91%, varying by infecting species and endemic region[35–38]; treatment in OWCL produces cures in 86–92%, but experience is quite limited.[39,40] Miltefosine is available in 10- and 50-mg capsules, and it is given at approximately 2.5 mg/kg per day (up to 150 mg/day) (Table 3). In practice, recommended dosing in adults with all forms of leishmaniasis translates to 150 mg/day for patients weighing > 45 kg. Drug is taken in divided doses with meals to diminish nausea, vomiting, and/or diarrhea, common reactions during the first week of treatment (Table 4). Serum chemistries should be monitored one time per week because of potential but fully reversible mild nephro- or less often, hepatotoxicity.[2,20]

TREATMENT OF MUCOSAL INFECTION

Occasionally reported outside of Latin America, mucosal disease complicates up to 5% of cases of NWCL caused by *Viannia* spp., primarily *L. braziliensis* and *L. panamensis*.[1,2,4] ML is seldom encountered in the United States and has mimicked inflammatory or even neoplastic disease in periodic case reports. Although ML is a late clinical manifestation, early mucosal involvement in NWCL may not be infrequent,[41] and travelers returning from South America may simultaneously show cutaneous and mucosal lesions.[10,11]

Twenty-eight days of miltefosine therapy produce a satisfactory response in ~80% of patients with mild ML and ~60% in severe disease.[28] Thus, miltefosine represents a reasonable alternative to the conventional treatment approach (28 days of sodium stibogluconate), to which 60–90% of patients respond (Table 3).[2,4] (A Phase III trial of miltefosine versus pentavalent antimony [meglumine antimoniate] is underway in Brazil.) Responses are measured 6–12 months after therapy using specified clinical criteria and sufficient time to detect relapse.[4,28] Liposomal amphotericin B, used at 20–35 mg/kg (total dose), may also be active, but reported experience in ML is very limited.[11,29,33]

TREATMENT OF VISCERAL INFECTION

Liposomal amphotericin B represents first-line treatment of VL in the United States and southern Europe. Although much less well-studied, amphotericin B lipid complex (Abelcet; Enzon Pharmaceuticals, Piscataway, NJ) and amphotericin B cholesteryl sulfate (Amphotec; Three Rivers Pharmaceuticals, Warrendale, PA) would also likely be effective.[2]

The seven-infusion, 21-day FDA-approved regimen for liposomal amphotericin B in immunocompetent patients with VL (Table 3) is inefficient, because total dose administered seems to be the key efficacy factor and not the number of infusions or duration of treatment.[2,19,27] Indeed, the particular pharmacokinetics and macrophage-targeted distribution of the liposomal formulation, along with good tolerability, opened the door to short-course therapy in VL and the use of up to 10 mg/kg per infusion.[2,19,27]

For US patients with VL acquired in the Indian subcontinent, delivering 10 mg/kg liposomal amphotericin B as a single dose[27] or 15 mg/kg through 5 consecutive day infusions of 3 mg/kg[2] should be effective (Table 3). For VL originally acquired in

TABLE 4
Common adverse reactions to selected antileishmanial agents[2,31]

Agent	Adverse reactions
Sodium stibogluconate	Abdominal pain, pancreatitis, or hyperamylasemia (28–97%), arthralgias/myalgias (49–59%), fatigue (19–67%), headache (22–44%), nausea/vomiting (12–20%), fever (17–22%), ECG changes (10–52%), increased LFTs (18–85%), or thrombocytopenia/leukopenia (11–44%)
Liposomal amphotericin B	Infusion-associated fever/chills (3–49%), nausea/vomiting or diarrhea (4–10%), rash (2–15%), back pain (2–10%), or increased creatinine (1–45%)
Miltefosine	Nausea/vomiting (6–76%), diarrhea (3–24%), headache (23–27%), motion sickness (29%), increased creatinine (1–32%), or LFTs (8–10%)

ECG = electrocardiograph; LFTs = liver function tests. Data are from review articles or representative treatment studies in all forms of leishmaniasis and include results from the following number of reports: sodium stibogluconate ($N = 6$), liposomal amphotericin B ($N = 5$), and miltefosine ($N = 7$). References available on request.

TABLE 5
Selected therapeutic approaches in cutaneous leishmaniasis[2,3,5–7,22–25,29,30,32,35–40,43]

Approach*	Comments
No treatment/observation alone	Reasonable, albeit not formally evaluated, in documented *L. mexicana* or *L. major* infection if no indication for treatment (Table 6) and lesions are small, spontaneously improving, and continue to heal.
Direct or topical treatment	
Intralesional pentavalent antimony	Likely effective but regimens are not standardized; produces local reactions.
Cryo- or thermotherapy	Produces local reactions; thermotherapy effective but requires local anesthesia.
Paromomycin ointment	Efficacy still controversial; new formulation being tested (not available in United States).
Parenteral chemotherapy	
Sodium stibogluconate	Effective with variable region- and/or species-specific efficacy; available through CDC IND and requires local IRB approval. Produces adverse reactions and requires monitoring during 10–20 days of administration (not for use in pregnant women).
Amphotericin B	
Deoxycholate	May be active in NWCL but little experience. Produces adverse reactions, and treatment is lengthy. Liposomal formulation clearly preferred (except for cost).
Liposomal	Limited information suggests activity in NWCL and OWCL using regimens active in VL; usually well-tolerated.
Pentamidine	In view of toxicity, no reason to use except perhaps for *L. guyanensis* infection.
Oral chemotherapy	
Miltefosine†	Variable region- and species-specific efficacy in NWCL; data limited in OWCL. Contraindicated in pregnant or breastfeeding women.
Imidazoles	
Ketoconazole	Thought effective, primarily in *L. panamensis* and *L. mexicana* infection, but seldom used as sole treatment in endemic regions or the United States.
Fluconazole	Not generally recommended, although higher doses may be active in OWCL (400 mg/day) and NWCL (8 mg/kg per day).

* Not recommended (little or insufficient efficacy in NWCL and/or OWCL in endemic regions): parenteral paromomycin, oral itraconazole, and oral azithromycin. NWCL = New World cutaneous leishmaniasis; OWCL = Old World cutaneous leishmaniasis; VL = visceral leishmaniasis.
† Not FDA-approved.

other regions, the therapeutic target should be a total dose of 18–20 mg/kg. In VL acquired in the Mediterranean region, two infusions of 10 mg/kg on consecutive days have been used successfully in children.[42] If liposomal amphotericin B could not be used, obtaining miltefosine would, on balance, provide a preferable alternative to sodium stibogluconate, unless immediate treatment was required or the patient was pregnant. High-level resistance precludes the use of sodium stibogluconate in VL acquired in Bihar State, India, where ~45% of the world's cases of kala-azar are found.[2]

Unless disease is well-advanced, most immunocompetent patients with VL respond well to therapy. Symptomatic improvement with resolution of fever usually occurs within the first week; within 2–4 weeks, spleen size is smaller, and pancytopenia improves.[2] A complete response (definitive cure) designation, however, is not assigned until six additional clinically unremarkable months have passed, the period in which most post-treatment failures (relapses) occur.[2,27]

TREATMENT OF CUTANEOUS INFECTION

Hastening resolution of active infection, reducing scarring, and decreasing the chance of recurrence are the goals of treatment in both NWCL and OWCL. For NWCL acquired in South America (where ~90% of cases are caused by *L. braziliensis*),[1] attempting to prevent mucosal disease is an additional objective. Tables 3, 5, and 6 summarize treatment approaches and generally accepted indications for initiating therapy in CL.

Although 70–88% of localized infections caused by *L. mexicana* (NWCL) or *L. major* (OWCL) heal spontaneously within 3–4 months,[2,22,44] treatment is given if an indication listed in Table 6 is present. In addition, although close observation alone is reasonable in selected cases, patients are often understandably uneasy with no immediate therapy. Thus, in practice in the United States, treatment of infections caused by *L. mexicana* or *L. major* is typically requested and given.

With the exception of NWCL caused by *L. guyanensis*, which may be less responsive,[2,3] daily treatment with sodium stibogluconate for 10–20 (OWCL) or 20 days (NWCL) is considered conventional. If infection caused by *L. major* or *L. mexicana* (which virtually never leads to ML) is treated, 10 rather than 20 days of therapy seems satisfactory.[2,3,43] Direct treatments (e.g., intralesional injections of sodium stibogluconate or formulations of topical paromomycin)[1–3] are used regularly in endemic regions as well as Europe and the United Kingdom. These and other direct treatments, including FDA-approved thermotherapy,[3] have been reported on or are being tested in this country.[22,43] However, few US civilian physicians are experienced in direct lesion treatments, and none would be appropriate in patients at risk for ML.

Ideally, clear-cut results from well-executed clinical trials would guide US clinicians to alternatives to sodium stibogluconate in CL. However, such information has been hard

TABLE 6
New and Old World cutaneous leishmaniasis: Indications for treatment[6,7,44]

	Indication for treatment
1	Infection acquired in South or Central America*
2	Cosmetically or functionally important lesion location (e.g., face, ear, hands, feet, or over joints)
3	Non-healing lesions (present for > 6 months)
4	Multiple (more than two to five lesions) or large lesions (> 4–5 cm)
5	Evidence of local dissemination of infection
6	Immunocompromised patient

* If no other indication (listed above) is present, treatment is not necessarily required in spontaneously improving, documented *L. mexicana* infection. In Old World cutaneous leishmaniasis, the same exception also applies to spontaneously improving, documented *L. major* infection.

to find.[23,24] Nevertheless, recent cumulative experience with miltefosine now seems sufficient enough to recommend its use as alternative initial therapy in NWCL[20,35–38] and probably OWCL.[39,40] Because cure rates vary in NWCL and experience is limited in OWCL, miltefosine-treated patients need to know that retreatment with another, less convenient agent may be necessary.

Although experience in CL with liposomal amphotericin B is also limited,[9,29,32,33] using the FDA-approved total dose for VL (21 mg/kg) in a more efficient regimen (e.g., seven consecutive one time per day infusions of 3 mg/kg) has similar appeal as an alternative to sodium stibogluconate.[32] Oral ketoconazole may also be an alternative initial therapy in NWCL caused by *L. panamensis* or *L. mexicana*.[45] If the infecting *Leishmania* strain in a patient with CL has not been identified, none of the preceding species-specific approaches or treatments (Tables 3 and 5) would be options. Reasonable assumptions about the responsible species can, however, sometimes be made by knowing where infection was likely acquired. Nevertheless, in the absence of species identification, a full course of treatment using sodium stibogluconate, miltefosine or perhaps, liposomal amphotericin B should be given (Table 3).

With any treatment, physical manifestations in CL take time to improve, and progress may seem slow. Criteria for judging clinical improvement and successful therapy vary. However, by 4–6 weeks after effective drug treatment, most ulcers heal (reepithelialize); if not, lesion size should be diminished by at least two-thirds accompanied by clear-cut improvement in local inflammation.[2] If by 6–8 weeks after treatment, lesion size and number have not diminished appreciably, any additional observation should be brief while making preparations for different therapy. The overall response (e.g., extent of ulcer reepithelialization) is usually not formally measured until 12 weeks post-treatment, at which time decisions about continued observation versus retreatment can also be made. Because treated CL may relapse, complete responses are not assigned until 6 or preferably, 12 months after apparently successful therapy.

TREATMENT IN IMMUNOCOMPROMISED PATIENTS

A T cell (primarily CD4 cell)-dependent, Th1-type cytokine-driven inflammatory response is required in leishmaniasis for macrophage activation, inhibition of intracellular replication, and parasite killing.[2] This mechanism seems to impart multiple host defense effects: (1) spontaneous control of many infections, (2) amplification and enhanced durability of initial treatment responses, and (3) prevention of remote reactivation of spontaneously controlled or treated infection by maintaining residual intracellular parasites in a clinically quiescent state.[2,46]

Deficient T-cell mechanisms, especially resulting from reduced CD4 cell number, derail the preceding effects, undermining initial responsiveness to chemotherapy, durability of an apparent therapeutic response, and prevention of recrudescence. Best documented in VL and less often in CL and ML, two predictable settings compromise antileishmanial defense—advanced human immunodeficiency virus (HIV) disease and T-cell dysfunction induced by iatrogenic immunosuppression (Table 1).[2,12–14,46]

Although treatment failures and/or relapses in CL or ML associated with HIV coinfection or deficient T-cell function may occur,[12] it is not clear that standard therapeutic approaches should necessarily be modified. In contrast, responses in CD4 cell-depleted (e.g., < 200 CD4 cells/mm^3) HIV-coinfected patients with VL are different. These patients, mostly with reactivated infection, often have difficulty in tolerating antileishmanial agents, especially pentavalent antimony,[47] and with the possible exception of those patients given liposomal amphotericin B,[12,26,47,48] ~30–45% respond poorly to or entirely fail initial treatment.[12] In addition, in coinfected patients who do show clinical improvement, the post-treatment parasitologic effect is also often suboptimal. Thus, except for recent data from India (which paint an extraordinarily different, more optimistic picture),[48] initial clinical responses are not usually durable, and relapses are common unless remission can be maintained by optimizing highly-active antiretroviral therapy (HAART) in conjunction with suppressive antileishmanial therapy. However, regimens to prevent subsequent or repeated relapses are not well-standardized, and they do not necessarily meet with success over the long term.[12] If the HAART-induced CD4 cell count remains at > 200 cells/mm^3 for 6 months, it may be possible to discontinue antirelapse (maintenance) treatment.[12]

In HIV-associated VL, the notion that initially giving more drug and/or lengthening treatment duration will produce better early or long-term results has little firm basis. Nevertheless, the FDA-approved regimen for liposomal amphotericin B in this setting involves 10 infusions of 4 mg/kg (total dose of 40 mg/kg) given over 38 days.[26] It would seem just as reasonable to administer a conventional course of liposomal amphotericin B (Table 3) and in patients who show clinical improvement, begin a maintenance regimen (e.g., 5 mg/kg every 2–3 weeks).[12] How to best attempt to induce remission in an entirely unresponsive patient or one who experiences multiple relapses is unclear; logic suggests considering using both liposomal amphotericin B and miltefosine in such situations.[47] VL patients with preserved CD4 cell number but impaired T-cell function resulting from iatrogenic immunosuppression respond differently. Such patients include those patients in whom reactivation of prior subclinical infection was provoked by treatment with corticosteroids, cancer chemotherapy, an anticytokine agent, or most frequently, antitransplant rejection drugs.[2,13,14] Although some of these patients do not respond to initial therapy and/or experience early post-treatment relapse, overall, they respond surprisingly well and durably to conventional treatment regimens.[13] In addition and for unclear reasons, long-term suppressive antileishmanial therapy seldom seems necessary in treated transplant recipients who are maintained on immunosuppressive agents.[13] Experience with CL and ML in iatrogenically immunosuppressed individuals is too limited to judge if similar conclusions also apply to their responses to conventional treatment approaches.

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