

## Leishmania Vaccines Entered in Clinical Trials: A Review of Literature

### Abstract

Leishmaniasis is considered as a zoonotic infection and neglected tropical disease. *Leishmania* treatment is not totally successful and imposes high expenditures, especially in developing countries. Since the natural infection leads to the robust immunity in most of the human cases, many bodies of research have been focusing on *Leishmania* vaccines, being capable to control *Leishmania* infection. First generation vaccines (such as Leishmune® and CaniLeish®) have proved robust protective immunity in dogs. In human, recombinant vaccines, including Leish-F1 could confer some degrees of protective immunity against natural infection. Recently, ChAd63-KH DNA vaccine has been accomplished in providing prevention against *Leishmania* infection; however, this vaccine should be further evaluated in other clinical trials.

**Keywords:** *Leishmania amazonensis*, *Leishmania donovani*, *Leishmania major*, *Leishmania mexicana*, *Leishmania vaccines*

### Introduction

Leishmaniasis, which is considered as a zoonotic and vector-borne protozoan infectious disease, transmits through >70 species of female sand flies assigned to *Phlebotomus* or *Lutzemia* genera.<sup>[1,2]</sup> This infection is second to *malaria* in its prevalence while 0.7–1.5 and 0.2–0.4 million new cases of cutaneous and visceral leishmaniasis (CL and VL) are annually reported.<sup>[3-5]</sup> Golden standard of *Leishmania* treatment is based on antimonial drugs; nevertheless, this approach is toxic and sometimes fails to achieve patient recovery due to antimicrobial resistance.<sup>[6,7]</sup> Furthermore, antimonial treatment imposes high expenditures, especially in the developing countries and the patients may poorly comply with the treatment regimen.<sup>[8-11]</sup>

On the other hand, natural infections of CL and VL dominantly cause robust immunity; hence, different studies have aimed to develop appropriate *Leishmania* vaccines. In the current study, we try to make a presentation of *Leishmania* vaccines, which are more likely to impact epidemiological aspect of this parasitological disease in the next coming years. Therefore, we aimed to focus on vaccines assessed in human clinical trials or animal field studies.

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### First generation vaccines

First generation antileishmanial vaccines comprises of three main subgroups: whole-killed parasites (i), fractionated *Leishmania* antigen (ii), Live-attenuated pathogens.

#### Whole-killed parasites

##### Killed *Leishmania* vaccines in new world

Whole-killed *Leishmania* vaccines have low cost and achieved the first senior success in animal modeling; nevertheless, none of the human vaccines in this subgroup has accomplished the World Health Organization (WHO) validity.<sup>[12]</sup> For instance, Leishvaccine, which comprised whole-killed promastigotes of *Leishmania amazonensis* (*L. amazonensis*) strain (IFLA/BR/1967/PH8) and Bacillus Calmette–Guérin (BCG), could play a prominent role in the protection of canine Leishmaniasis. In fact, this vaccine induced a significant increase in a mixed cytokine pattern. The vaccine stimulated innate immunity (especially neutrophils and eosinophils) and activated CD4+T, CD8+T, and B cells [Figure 1].<sup>[13]</sup> Leishvaccine in human was successfully applied in Phase I and II of clinical trials, which well documented its safety and immunogenicity; however, this vaccine failed to achieve satisfactory results

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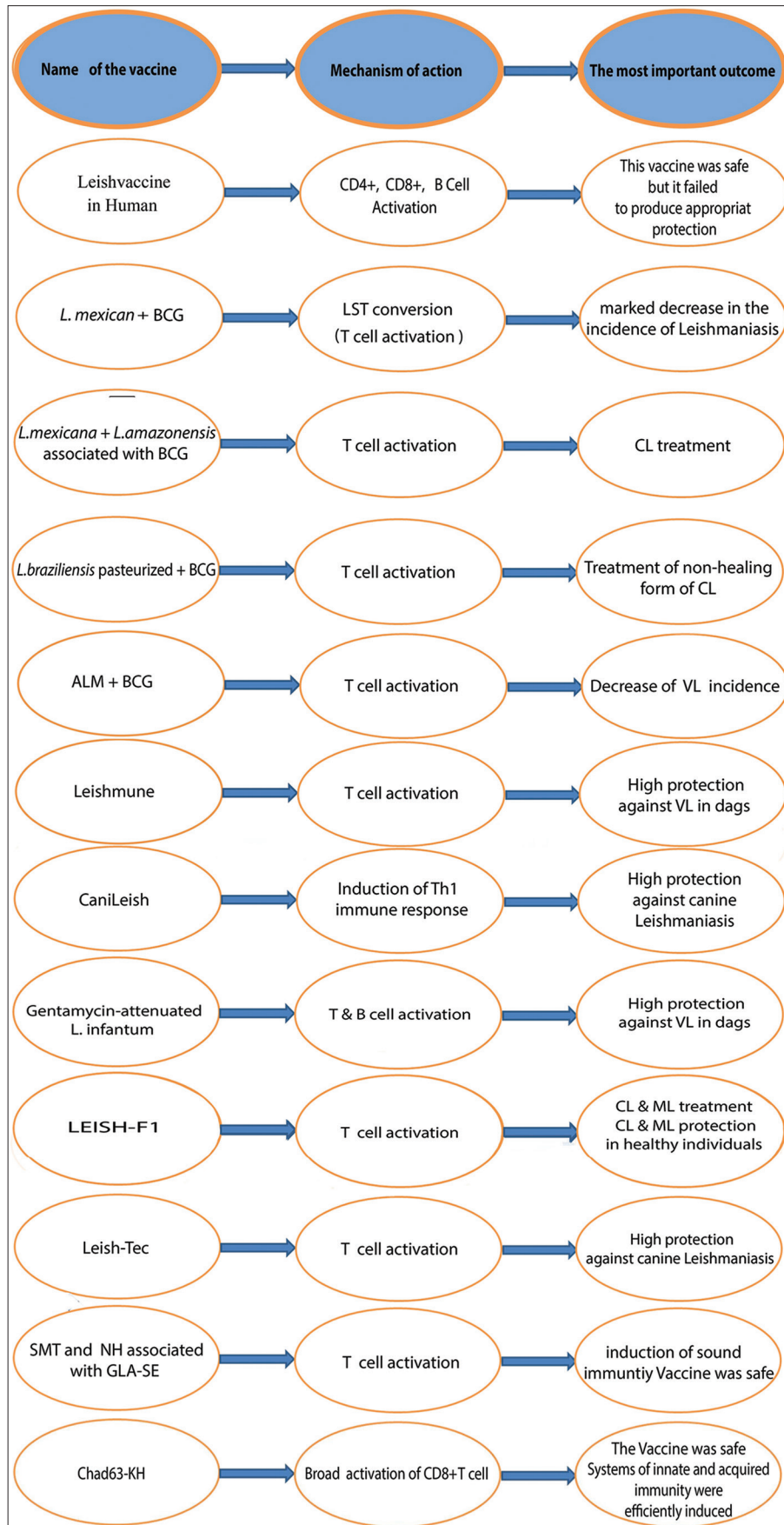


Figure 1: Diagram showing mechanism of action and the most important outcome of the vaccines

in Phase III of the randomized clinical trial (RCT) [Figure 1 and Table 1].<sup>[14]</sup>

In different studies, the efficacy of autoclaved-killed *Leishmania mexicana* (*L. mexicana*) associated with BCG was assessed for both prophylaxis and immunotherapy aims.<sup>[15]</sup> The vaccine application resulted in low levels of leishmanin skin test (LST) conversion; however, it was noticeable that the incidence of Leishmaniasis significantly decreased in LST-converted participants.<sup>[15]</sup>

As a promising approach, a composite of two endemic species (*L. mexicana* and *L. amazonensis*) associated with BCG protected 73% of healthy individuals in the Republic of Ecuador.<sup>[16]</sup> To assess the immunotherapy effects of the above vaccine (*L. mexicana* + *L. amazonensis* associated with BCG), 11,532 CL patients were recruited in a multicenter RCT implemented over 10 years. All of the recruited patients were afflicted with localized CL (LCL) and preliminary diagnosis was based on the LST conversion. In that study, the majority of the patients with CL were treated with almost no side effects and the treatment protocol was cost effective [Figure 1].<sup>[17]</sup>

The immunotherapy strategy achieved further success in the patients afflicted by mucocutaneous and diffuse forms of CL. They were treated with promastigotes of *Leishmania braziliensis* (*L. braziliensis*) killed by pasteurization and associated with viable BCG. This kind of immunotherapy

offered a safe option in severe forms of CL, which did not respond to conventional chemotherapy. In comparison with autoclaved-killed *Leishmania* vaccines, pasteurization method achieved further efficacy since protein components of pasteurized and fresh promastigotes did not significantly differ. In Venezuela, pasteurized *L. braziliensis* + BCG is currently applied for the treatment of the non-healing form of CL, which does not respond to three courses (2 months) of antimonial treatment [Figure 1].<sup>[15]</sup>

In general, vaccination with killed *Leishmania* promastigotes could be considered as a safe and economical treatment; nevertheless, further trials aiming at evaluation of different adjuvants potentially pave the way for more efficient vaccines.<sup>[18]</sup>

### Killed *Leishmania* vaccines in old world

In the old world, *Leishmania major* (*L. major*), as an immunogenic component, has been used in different clinical trials aiming at *Leishmania* treatment and prevention.<sup>[15]</sup> For instance, autoclaved-killed *L. major* (ALM) associated with BCG was evaluated in Phase I and II clinical trials implemented among healthy participants living in non-endemic areas of CL. Though the safety of the vaccine formula was approved, LST conversion occurred in just about 38% of the healthy participants and low levels of interferon-gamma was produced in response to soluble *Leishmania* antigen (SLA) [Figure 1].<sup>[12,19]</sup>

For further investigations, this vaccine was also assessed in healthy volunteers living in endemic areas of CL such as Bam (Kerman Province, Iran). The vaccine application led to LST conversion occurring in a small proportion of healthy participants (16.5%). In another clinical trial, a booster dose of the ALM vaccine associated with BCG was used in Sudan and the results of the study indicated a significant decrease (43%) of VL incidence in LST-converted individuals [Figure 1].<sup>[12,19,20]</sup>

In addition to preventive aims, ALM has also been used in clinical trials to assess what effects it might have. For example, in Sudan, a composition of sodium stibogluconate (Stb) and alum-precipitated ALM (alum/ALM) + BCG was used for the treatment of post-kala-azar dermal leishmaniasis (PKDL). The results of that study showed that the combination of the *Leishmania* vaccine and Stb was more efficient, compared with Stb alone (53% vs 87%) [Figure 1].<sup>[15,21]</sup>

### Fractionated *Leishmania* antigens

Two fractionated vaccines, which are called Leishmune<sup>®</sup> and CaniLeish<sup>®</sup>, have achieved impressive success in the prevention of canine Leishmaniasis. These veterinary licensed vaccines protect dogs and block *Leishmania* transmission from dogs to human arising from sand fly biting [Figure 1].<sup>[22]</sup>

Leishmune<sup>®</sup> is based on fucose-mannose ligand (FML) and saponin as an adjuvant. FML, which is expressed

**Table 1: Status of *Leishmania* vaccines entered in clinical trials**

| Vaccine name                       | Classification    | Phase I | Phase II | Phase III | Reference |
|------------------------------------|-------------------|---------|----------|-----------|-----------|
| Leishvaccine                       | First generation  |         |          | x         | [14]      |
| ALM <sup>p</sup>                   | First generation  |         | x        |           | [19]      |
| Leishmune                          | First generation  |         |          | x         | [22]      |
| CaniLeish                          | First generation  |         |          | x         | [23]      |
| GALM <sup>a</sup>                  | First generation  |         | x        |           | [28]      |
| LEISH-F1                           | Second generation | x       |          |           | [30]      |
| LEISH-F2                           | Second generation |         | x        |           | [32]      |
| LEISH-F3                           | Second generation | x       |          |           | [33]      |
| Leish-Tec                          | Second generation |         |          | x         | [36]      |
| SMT <sup>γ</sup> + NH <sup>μ</sup> | Second generation | x       |          |           | [38]      |
| ChAd63-KH                          | Third generation  |         | x        |           | [40]      |

p=Autoclaved-killed, *L. major* a=Gentamycin-attenuated *L. major*; γ=Enzyme sterol 24-c-methyltransferase, μ=Nucleoside hydrolase

in all cycles of *Leishmania* species, can be used as a suitable antigen in dog and human serodiagnosis. FML of Leishmune<sup>®</sup> has been purified from *Leishmania donovani* (*L. donovani*) promastigotes and saponin part of the vaccine includes QS21 and two deacylated saponins. The efficacy of Leishmune<sup>®</sup> was approved in endemic areas of Brazil, where 92–97% of the vaccinated dogs were protected against canine VL [Figure 1].<sup>[12,22]</sup>

LiESP/QA-21 vaccine or CaniLeish<sup>®</sup> (CaniLeish, Virbac, France) is the only *Leishmania*-licensed vaccine in Europe. This vaccine was produced through extracted secreted proteins of *Leishmania infantum* (LiESP). These purified proteins were derived in cell and serum-free culture patented by the Institut de Recherche pour le Développement (IRD). Furthermore, this protein was associated with a highly purified part of a fraction of saponin, which was called QA-21. The dogs vaccinated with CaniLeish<sup>®</sup> could develop Th1 immune response within 3 weeks [Figure 1].<sup>[23-25]</sup>

It seems that the fractionated *Leishmania* vaccines could be efficiently used in areas where there is a crucial need for the control of the *Leishmania* infection [Figure 1].<sup>[26]</sup>

### Live-attenuated pathogens

Some research has shown that live attenuated form of *Leishmania infantum* (*L. infantum*) could be considered as an appropriate tool for the prevention of the canine Leishmaniasis.<sup>[27]</sup> In this regard, a field study was conducted among 103 dogs, grouped vaccinated ( $n = 55$ ) and control ( $n = 44$ ) trials. The process of *Leishmania* culture was done under the pressure of gentamicin (20 µg/ml). All of the dogs were not exposed to *Leishmania* infection, living in non-endemic areas of Iran. After the vaccination, all of the dogs were moved to Baft (Kerman, Iran), recognized as an endemic area of *L. infantum*. They were followed up for 24 months, experiencing four sand fly seasons (June and September).<sup>[27]</sup> At the end of the experience, the specific antibody for *Leishmania*-antigen wild type was found in 32% of the non-vaccinated dogs, whereas there was not any positive sample in the vaccinated group.<sup>[27]</sup> Clinical signs of Leishmaniasis were found in 29% and 2.2% of the control and vaccinated dogs, respectively [Figure 1].<sup>[27]</sup>

Documenting sound immunity of gentamycin-attenuated *L. infantum*, there is a real prospect that live-attenuated vaccines are capable to curb canine *Leishmania* infection in the near future.<sup>[27]</sup> In this regards, there is an ongoing clinical trial, aiming to employ gentamycin-attenuated *L. major*, has been implemented. This randomized and double-blind clinical trial was designed to assess the safety and protective effects of the *L. major* vaccine [Table 1].<sup>[28]</sup>

### Second generation vaccines

Recombinant proteins, which are produced through genetically engineered-cells, are termed as “second generation vaccines.” LEISH-F1, formerly called Leish-111f, which has reached the Phase II of clinical trials. This artificial protein is encoded by three genes: *L. major* homologue of eukaryotic thiol-specific antioxidant (TSA), *L. major* stress-inducible protein-1 (LmSTI1), and *L. braziliensis* elongation and initiation factor (LeIF). This protein was produced by the Infectious Disease Research Institute (IDRI, Seattle, WA, USA) and emulsified with an adjuvant called “monophosphoryl lipid A in structure stimulating Toll-like receptor (TLR)” (MPL-SE). Not only could LEISH-F1+ MPL-SE efficiently treat patients afflicted by CL or ML, but also this vaccine efficiently induced protective immunity in healthy volunteers [Figure 1].<sup>[4,29-31]</sup>

In a different study, IDRI has launched another artificial protein, called LEISH-F2.<sup>[29]</sup> This protein excludes N-terminal histidine tag, resulting in more resemblance to natural proteins of wild species.<sup>[29]</sup> In addition, due to the substitution of glutamine for Lys274, the manufacturing process of LEISH-F2 has been improved, compared with LEISH-F1.<sup>[29]</sup> After safety and immunogenicity approval, the vaccine entered Phase II of a clinical trial, where its therapeutic effects on CL patients were assessed and compared with chemotherapy.<sup>[29]</sup> For this aim, LEISH-F2 (10 µg) was associated with MPL-SE adjuvant (25 µg) and the period of the clinical cure was determined for every patient.<sup>[29,32]</sup>

LEISH-F3 is another multicomponent vaccine comprised of two proteins: nucleoside hydrolase (NH) and sterol 24-c-methyltransferase (SMT), derived from *L. donovani* and *L. infantum*, respectively.<sup>[33]</sup> The vaccine was formulated with a TLR-4 ligand, namely glucopyranosyl lipid A-stable oil-in-water nanoemulsion (GLA-SE).<sup>[33]</sup> The application of the vaccine in healthy and adult individuals, living in Washington (US), showed promising results as a robust immune response against VL was induced.<sup>[29,33-35]</sup>

Leish-Tec<sup>®</sup>, licensed as a second generation vaccine in Brazil, contains A2 antigen of *L. infantum*. In a field trial, which was implemented among 847 seronegative dogs in southeastern part of Brazil, the dogs were assigned to either control ( $n = 418$ ) or interventional ( $n = 429$ ) group. The interventional group received three doses of the vaccine with 21-day intervals. Every single dose of the vaccine included 100 µg/mL of recombinant A2 protein and 500 µg/mL of saponin, which was applied as an adjuvant. The control group received a placebo. All of the dogs were followed up for 18 months through serological and parasitological methods. The results of that study showed that Leish-Tec<sup>®</sup> could efficiently prevent the incidence of canine Leishmaniasis among the dogs, which were naturally exposed to *Leishmania* parasite [Figure 1].<sup>[36]</sup>

Two recombinant proteins called “enzyme sterol 24-c-methyltransferase” (SMT) and “nucleoside hydrolase” (NH) can also be assumed as appropriate candidates for vaccine development.<sup>[34,37]</sup> SMT and NH sequences not only are conserved among *Leishmania* species but also do not exist in homospecies. The combination of SMT and NH proteins called NS was formulated with “glucopyranosyl lipid A-stable oil-in-water nanoemulsion” (GLA-SE), which was considered as a potent TLR-4 ligand. This structure was applied in a Phase I clinical trial study performed among healthy and uninfected individuals living in the USA. The results of the study showed that the combination of NS protein and GLA-SE adjuvant could induce safe and robust immunity against *Leishmania* infection [Figure 1].<sup>[34,37]</sup>

### Third generation vaccines

Documenting the beneficial role of CD8<sup>+</sup> T cells in the treatment and prevention of VL and PKDL, many bodies of research have been focusing on DNA vaccines.<sup>[38]</sup> In a very recent study, it was shown that a third generation vaccine, employing semian adenovirus (ChAd63) could effectively elicit a wide range of CD8<sup>+</sup> T cells, specified for *Leishmania* antigens.<sup>[38]</sup> This vaccine encoded KH gene, constituted of two genes of *L. donovani* antigens: KMP-11 and HASPB.<sup>[38]</sup> The results of the study showed that not only intramuscular doses ( $1 \times 10^{10}$  and  $7.5 \times 10^{10}$  ChAd63-KH) of ChAd63-KH were safe but also it efficiently induced interferon-gamma production and dendritic cell activation.<sup>[38]</sup> As a result, the application of ChAd63-KH vaccine as a promising approach for the prevention and treatment of *L. donovani* infection [Figure 1].<sup>[38]</sup>

In this regard, researchers have been evaluating the therapeutic effects of ChAd63-KH in Phase II of a non-randomized trial [Table 1].<sup>[39]</sup> This clinical trial has aimed to assess vaccine safety, as well as its cellular immune response and clinical changes in PKDL patients.<sup>[39]</sup>

### Conclusions

Many bodies of research aimed to fulfill the hopes for an appropriate *Leishmania* vaccine; nevertheless, a small fracture of them has been found as a promising approach for *Leishmania* treatment and prevention. Dogs are considered as the primary reservoir of *Leishmania* infection and the animal vaccination can clearly impact the burden of the disease in the human population. Hence, animal vaccines such as Leishmune®, CaniLeish®, and Leish-Tec could be recommended as appropriate choices for the control and prevention of Leishmaniasis. Furthermore, second-generation vaccines such as LEISH-F2 could be adopted as a promising approach for the prevention of human Leishmaniasis. Recently, live attenuated and DNA vaccines have induced appropriate immune response against *L. infantum* and *L. donovani*

infections, respectively. As a result, these vaccines could be considered as promising approaches to the prevention of *Leishmania* infections.

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### Conflicts of interest

There are no conflicts of interest.

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