

Comparative aspects of immunity and vaccination in human and bovine trichomoniasis: a review

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Abstract *Trichomonas vaginalis* and *Tritrichomonas foetus* are important extracellular protozoans that cause, respectively, human and bovine venereal diseases. Trichomonads are extracellular parasites that primarily inhabit the genital tracts of the mammalian hosts where they overcome the mucus barrier and parasitize mucosa by contact-dependent or contact-independent cytotoxicity. Transient immunity is usually achieved by the host after clinical infection. At present, vaccination in cattle reduces infection rates and reproductive wastage in affected herds. After vaccination, immunoglobulin G (IgG) levels increase in systemic circulation while immunoglobulin A (IgA) levels rise in the vagina. Only moderate protection is conferred by means of vaccination. Future vaccine development strategies are needed for cattle to enhance the antigenic component or use adjuvant that strongly activates the innate immune response to produce safe and potent vaccines. This paper reviews the current knowledge of the immunology of trichomoniasis infection and the challenges and potential of vaccines in the control of the infection in human and bovine trichomoniasis.

Keywords *Tritrichomonas foetus* · *Trichomonas vaginalis* · Venereal infection · Immunity · Vaccination · Bovine · Fertility

Introduction

Trichomoniasis is an important human and bovine sexually transmitted infection (STI) caused by fastidious flagellated trichomonad protozoans in the phylum Parabasalia, order Trichomonadida, and family Trichomonadidae (Brugerolle and Lee 2000). The human pathogen, *Trichomonas vaginalis*, is primarily an infection of the urogenital tract residing in the vagina and urethra and causing vaginitis, cervicitis, and pregnancy losses. This perturbation of the genital cell membranes predisposes women to an increased risk of transmitting human immunodeficiency virus (HIV) (Petrin et al. 1998). Similarly, infection with *Tritrichomonas foetus* in cattle is devastating and causes vaginitis, cervicitis endometritis, and sub-fertility (Rhyan et al. 1988).

Morphologically, trichomonads are complex single-celled organisms that multiply by binary fission. These protozoa are approximately twice the size of white blood cells and are highly motile; *Trichomonas vaginalis* has four anterior flagella while *Tritrichomonas foetus* has three (Benchimol 2009). Both have a recurrent flagellum that runs toward the posterior region of the cell adhering to the cell body to form an undulating membrane (Honigberg 1978). Both are extracellular parasites which penetrate the mucus barrier and parasitize the genital epithelium. Cyto-adherence is necessary for pathogenicity (Arroyo et al. 1995; Mendoza-Lopez et al. 2000). In the reproductive tract, the trichomonads colonize and establish an infection by adhering to the vagina and then subsequently ascending to the cervix and uterus (Mendoza-Lopez et al. 2000). This progressive invasion of the genital tract results

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in varying degrees of inflammation with consequent transient or permanent sterility (BonDurant 1997). Although current therapies use nitroimidazole drugs in both humans and cattle to control infection, some adverse side effects, poor availability, and treatment failures are known to reduce efficacy (Kulda 1999; Wendel and Workowski 2007).

The role of acquired immunity in preventing human trichomoniasis is still not clearly understood. Some reports showed that exposures to *Trichomonas vaginalis* do not confer protection (Petrin et al. 1998). Repeated infections with *Trichomonas vaginalis* can occur without significant decrease in either the duration of infection or the severity of symptoms (Honigberg 1978; Garber and Lemchuk-Favel 1990). Recent studies proved that transient immunity can be achieved after *Trichomonas vaginalis* infection in women (Chang et al. 2004) and *Tritrichomonas foetus* infection in cows (Corbeil et al. 2008). Vaccination against *Tritrichomonas foetus* is beneficial in cattle because it results in formation of inductive sites for a local IgA response genital mucosa (Villarroel et al. 2004) and therefore has great potential as a strategy for combating trichomoniasis.

This review discusses the pathogenesis, the host immune responses, and the role of immunotherapy in the control of human and bovine genital trichomoniasis. The potential for the development of an effective vaccine is also highlighted.

Economic importance

About 340 million cases of human sexually transmitted infection (STI) are diagnosed annually (Garcia Vega and Puigvert Viu 2010) of which 51.2 % (174 million cases) are trichomoniasis making it the most common non-viral STI in the world, particularly the developing countries (Mavedzenge et al. 2010; Onoya et al. 2012). The prevalence of *Trichomonas vaginalis* infection in the USA is estimated to be 2.3 million (3.1 %) among women ages 14–49 years (Sutton et al. 2007)

In cattle in the USA, *Tritrichomonas foetus*-infected bulls in a herd cost \$US800–6030 per bull per year (Williamson 2009; Fitzgerald 1986). Infection in cows causing early embryonic death, abortion, pyometra, or transient infertility is worth losses of \$US 60 million per annum when 25 % of the herds are endemically infected (Hum 1996). The economic impact of trichomoniasis infection is therefore severe; the calf crop can be reduced by up to 50 % in beef enterprises.

Clinical manifestation in humans

Nearly 50 % of women with *Trichomonas vaginalis* are asymptomatic (Swygard et al. 2004, Romoren et al. 2007), and the extent of the inflammatory responses to the parasite determines severity of the symptoms. There are reports of

dysuria, lower abdominal discomfort, itchiness of the vagina, leucorrhea, and vaginal odor in some women (Schwebke and Burgess 2004). Thus, *Trichomonas vaginalis* infection is usually only detected during routine STD screening (Bosserman et al. 2011).

Trichomoniasis is also prevalent in men, especially the partners of infected women. Unlike in women, the condition usually resolves without treatment within 2 weeks to 4 months (Krieger 1995). The high rate of asymptomatic infection in men means that many people unknowingly harbor the parasite and spread the infection within the community. It is thought that high zinc concentrations found in men may prevent *Trichomonas vaginalis* from being established in the male reproductive tract because *Trichomonas vaginalis* is readily killed at concentrations of zinc that occur in the prostatic fluid of healthy men (Langley et al. 1987).

Clinical manifestation in cattle

On the other hand, clinical outcome of *Tritrichomonas foetus* infection in cows includes early embryonic death, abortion, fetal macerations, and/or pyometra. Some cows, following abortion, are temporarily infertile or become carriers (Rae 1989). In contrast to humans, pregnancy losses (early embryonic death, repeat breeding, abortion) are typical clinical manifestations. Campylobacteriosis presents similar clinical signs in cows and is often confused with trichomoniasis (Dijkstra et al. 2005; Bergen et al. 2005; Hoffer 1981; Bawa et al. 1987; Hum 1987; Wittenbrink 2002). Observant owners report early return to estrus as the first clinical sign of *Tritrichomonas foetus* infection during the breeding season. Pyometra and fetal maceration are usually incidental findings during transrectal palpation for pregnancy diagnosis.

The absence of macroscopic and microscopic pathology and a limited immunologic response to *Tritrichomonas foetus* infection in bulls mean that no overt clinical signs are exhibited by infected bulls (Bondurant 2005).

Pathogenesis

The pathogenesis of trichomonad infection is not well understood (Bachmann et al. 2011; Cobo et al. 2011a, b; Hirt et al. 2011). Cyto-adherence (Alderete et al. 1995) and cytotoxicity (Petrópolis et al. 2008; Ramon-Luing Lde et al. 2011) are thought to be the principal mechanism. Binding of trichomonads to vaginal epithelial cells for colonization and infection is dependent on adhesion molecules on the surface of the parasites, either alone or with other soluble parasite molecules such as hydrolytic enzymes (Peterson and Alderete 1982; Neale and Alderete 1990; Lockwood et al. 1984; Hernandez et al. 2011), cytotoxic molecules (Ramon-Luing Lde et al.

2011; Lucas et al. 2008), cell detaching (Garber et al. 1989), or cell lytic factors (Alvarez-Sanchez et al. 2000; Kennett et al. 2002).

In human trichomoniasis, a complex relationship between *Trichomonas vaginalis* growth and the *Lactobacilli* bacteria in the vagina is thought to influence clinical outcome (Bachmann et al. 2011; Meysick and Garber 1992). It is not clear whether *Trichomonas vaginalis* infection alters the vaginal microenvironment by creating an anaerobic situation or if anaerobes in the vagina precede *Trichomonas vaginalis* growth (Petrin et al. 1998).

In laboratory mice, *Tritrichomonas foetus* maintains its shape and flagella and adheres to and injure vaginal and endometrial epithelial cells (Singh et al. 2004; Gilbert et al. 2000; Midlej et al. 2009; Vilela and Benchimol 2011; Pereira-Neves et al. 2012). Inhibition of cell division and endometrial inflammation were detected in vitro in oviduct organ culture models (Benchimol et al. 2006; Ma et al. 2011).

Tritrichomonas foetus invades bovine placental tissue (Rhyan et al. 1988) causing inflammatory changes in the endometrium and oviducts (Anderson et al. 1996). The interactions of *Tritrichomonas foetus* and *Trichomonas vaginalis* with host epithelial cells are associated with the activation of different proteases causing epithelial cell apoptosis (Midlej et al. 2009; Midlej and Benchimol 2010). In vivo, *Tritrichomonas foetus* initially adheres to and infects the vagina, causing vaginitis, and then ascends to the uterus and oviduct (Anderson et al. 1996; BonDurant et al. 2003) and may also cross the placenta. Trichomonads are usually confined to the lumen of the genitalia (Parsonson et al. 1976) but can adhere tightly to oviductal epithelial cells, thus preventing fertilization (Midlej et al. 2009). On the other hand, *Trichomonas vaginalis* causes hydrolase and endotoxin invasion of the amniotic fluid in pregnant women (McGregor et al. 1992).

In the murine model, *Tritrichomonas foetus* maintains its shape and flagella when invading the deeper oviduct folds which are better suited for anaerobic respiration (Monteavaro et al. 2007) while *Trichomonas vaginalis* assumes an amoeboid shape when adhering to epithelial cells (Gonzalez-Robles et al. 1995).

Pathological signs and symptoms

Post-insemination pyometra occurs in about 10 % of the cows. Infection is established through colonization of the vagina by the trichomonad and then ascends to the uterus (Rae and Crews 2006). After an incubation period of 3–22 months, clinical signs in heifers include vaginitis; endometritis; and edema of the vulva, perivaginal tissue, and uterine wall (Parkinson 2009). Fertilization and implantation are not disturbed, but the conceptus dies around 30–50-day gestation

(Parsonson et al. 1976) while some abort as late as 5 months (Rae and Crews 2006). Many cows successfully eliminate the infection after calving (Parkinson 2009; Skirrow 1987).

Infection of the bull is venereal and asymptomatic (Parsonson et al. 1974; Rhyan et al. 1999a). Bulls 5 years or older often become lifelong carriers because the deep crypts of the penile integument and preputial mucosa provide a suitable niche for the parasite. Urethritis is sometimes seen while purulent urethritis was reported in men with acute *Trichomonas vaginalis* infection (Petrin et al. 1998; Abdolrasouli et al. 2007; Saleem et al. 2009; Le Roux et al. 2010).

Immunization in humans

The roles of convalescent or acquired immunity in human trichomoniasis are not clear. Repeated infections with *Trichomonas vaginalis* occur without a significant decrease in either the duration of infection or the intensity of symptoms as might be expected in the presence of a specific immune response (Honigberg 1978; Garber and Lemchuk-Favel 1990). Anti-*Trichomonas vaginalis* immunoglobulins (IgM, IgG, and IgA) titers rise after *Trichomonas vaginalis* infection, but there is no specific protection (Abraham et al. 1996). Although anti-trichomonal antibodies are present in human cervicovaginal secretions (Ryan et al. 2011), there is no evidence that local vaginal immunoglobulins play a role in protection against *Trichomonas vaginalis* infection. Thus, the role of cell-mediated immunity in vivo is not clear (Yano and Kurata 2011).

In field trials using heat-inactivated *Trichomonas vaginalis* vaccine prepared from inactivated lactobacilli and administered intravaginally, persistently infected women were clinically cured (Aburel et al. 1963; Milovanovic et al. 1983; Gombosova et al. 1986; Demes et al. 1985; Cudmore and Garber 2010). However, lack of antigenic similarity between the vaccine and *Trichomonas vaginalis* was reported (Alderete 1988) while other trials with the vaccine were inconclusive (Guerrero et al. 1987). It is not clear why this vaccine is less effective than the bovine vaccine. Infection in human and cattle needs to be further investigated.

An in vitro study showed that mice became immune when *Trichomonas vaginalis* was injected subcutaneously with Freund's complete adjuvant and a booster dose with the trichomonads and Freund's incomplete adjuvant (Abraham et al. 1996). Thus, systemic vaccination increased antibody (IgG) and cytokine production and increased proliferation and/or maturation of immune cells compared to vaginally infected naïve mice (Abraham et al. 1996). Vaccinating mice with *Trichomonas vaginalis* (subcutaneous injection of whole cells with adjuvant) protects from subsequent vaginal infection, indicating long-term immunity (Martinotti et al. 1977; Paintlia et al. 2002). Molecular expression of pro-

inflammatory cytokines, markers for T regulatory and T helper 17 cells, as well as heme oxygenase-1 expression in uterine tissue of BALB/c mice has demonstrated TNF- α augmentation in the uterus of infected animals. Anti-inflammatory cytokine IL-10 was also upregulated (Vilela and Benchimol 2013; Woudwyk et al. 2012). These studies provide new hope for development of vaccines against trichomoniasis.

Hindrance to developing solid immunity is the heterogeneous immune responses to *Trichomonas vaginalis* infection (Garber et al. 1986). Serum from infected women had antibodies against different protein epitopes despite receiving the same trichomonal strain (Garber et al. 1986).

Convalescent and acquired immune responses to *Tritrichomonas foetus* infection reveal an ability to mount innate responses by the host at a local and systemic level (Anderson et al. 1996; Clark et al. 1983a; Skirrow and BonDurant 1990; BonDurant et al. 1993; BonDurant et al. 1996; Corbeil et al. 1998). Antigen uptake by the genital epithelia is followed by formation of mucosal-associated lymphoid tissue and local IgA and IgG 1 response. In cattle, infected heifers mounted minimal systemic antibody responses but strong vaginal, cervical, and uterine IgA and IgG1 responses 7–12 weeks after an intravaginal inoculation of *Tritrichomonas foetus* (BonDurant et al. 1996; Corbeil et al. 1998). Thus, whole-cell and subunit vaccines provide protection when administered either systemically or intravaginally to susceptible females (Hudson et al. 1993; Corbeil 1994).

Other vaccine strains also successfully provoked both local and systemic immune responses in virgin heifers after mucosal (intravaginal/intranasal) or systemic administration (BonDurant et al. 1993; Ikeda et al. 1995; Voyich et al. 2001). TF190 adhesin, a glycoprotein surface component of *Tritrichomonas foetus* (Shaia et al. 1998), the immunoaffinity-purified superficial antigen *Tritrichomonas foetus* 1.17 (Hodgson et al. 1990), showed efficacy. Systemic immunization with these antigens produced high titers of IgG antibody and primed anamnestic mucosal IgA response in heifers challenged with *Tritrichomonas foetus*. Vaccinated heifers also cleared infection faster than control animals. Thus, immunoprophylaxis reduces infection rates in cattle.

Systemic vaccination with killed *Tritrichomonas foetus* in oil adjuvant prevents infection in bulls aged 5 years but is not protective in older bulls (Clark et al. 1983b). Recent studies show that infected bulls have significantly more IgG1, IgA, IgM, and IgG2 antibodies to *Tritrichomonas foetus* 1.17 antigen in preputial secretions (Rhyan et al. 1999b; Cobo et al. 2010; Cobo et al. 2011a, b). However, in South Africa, attempts to use killed whole-cell TF systemic vaccination in bulls were not successful (Herr et al. 1991).

There are ongoing efforts to develop vaccines for human and bovine trichomoniasis (Cudmore and Garber 2010). In a field trial using a whole-cell vaccine, the immunity induced by the vaccine greatly reduced *Tritrichomonas foetus* infection

and reproductive loss (Schnackel et al. 1990). The reduction in the infection rate is associated with increased local and systemic anti-trichomonal antibodies in genital tract secretions of infected heifers (BonDurant et al. 1993; Campero et al. 1999; Campero and Cobo 2006).

A commercially available monovalent vaccine containing 5×10^6 killed cells, whole of *Tritrichomonas foetus* suspended in a special oil adjuvant, is partially protective (Kvasnicka et al. 1992). A comparison of pregnancy and calving rates between beef heifers vaccinated with this vaccine and control heifers showed that twice as many vaccinated heifers calved as control animals (61 vs 31 %) (Kvasnicka et al. 1992). The efficacy of this vaccine is yet to be tested on bulls (Bondurant 2005).

These responses to vaccination can be compared to those of bovine genital campylobacteriosis. Campylobacteriosis vaccines are available for immunotherapy and immunoprophylaxis of bovine genital campylobacteriosis (Bondurant 2005). High infection clearance rates following vaccination mean that immunotherapy of valuable bulls is clinically feasible (Bondurant 2005). The same vaccine is used prophylactically to either prevent infection or significantly reduce the persistence of infection in both bulls and cows (Cobo et al. 2011a, b; Bondurant 2005; Vasquez et al. 1983; Eaglesome et al. 1986; Corbeil et al. 2003). In addition, immunized bulls do not become permanent carriers of *Campylobacter foetus venerealis*.

All clinical vaccine trials show that it is beneficial to vaccinate cattle against trichomonosis (Villarroel et al. 2004; Schnackel et al. 1990; Kvasnicka et al. 1992). The promise of these current vaccines makes it imperative to continue the search for suitable vaccine immunostimulatory component, appropriate timing, and most effective and safe route of administration of vaccines to produce robust lifelong protection.

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