Autovaccination therapy in recurrent vulvovaginal candidiasis

Summary

20-30% of women affected by vulvo-vaginal Candidiasis frequently develops recurrences. Therapy and pharmacology prophylaxis have shown a high percentage of insuccess. Objective of the study was the evaluation of immunotherapy to prevent the recurrences of candida vaginitis. 74 women between 20-50 years old underwent treatment with an autogenous vaccine. Treated women had been suffering, from at least, four vaginitis episodes/year for at least 2 years and therapy and long-term pharmacological prophylaxis had any result during the year after the suspension. Sintomatology disappeared in 62 of the patients and 6 reported a relevant improvement. Laboratory follow-up showed absence of Candida in the vaginal secretion of 64 of 68 women who reported recovery or improvement. The approach with autovaccination may be an excellent alternative in recurrent vulvovaginal candidiasis. The results achieved are encouraging for the prosecution of the study based on the immunological approach to therapy and prophylaxis in fungal infections.

Introduction

Vaginal mycotic infection represent more than 50% of all vaginitis. 20-30% of women affected by vulvo-vaginal candidiasis frequently develops recurrent episodes and sometimes even chronicization. Therapy and long-term pharmacology prophylaxis have shown a high percentage (20 % ca.) of insuccess. Recurrent vulvo-vaginal candidiasis is defined as four or more episodes of infection per year, in only a minority the pathogenesis, including uncontrolled diabetes and immunosoppressive therapy, is apparent. Cell-mediated immunity and nonspecific cellular immunity are generally believed to provide the main defenses against fungi. The importance of cellular defense mechanism is supported by the clinical observation that most invasive fungal infections occur in individuals with defective cellular immunity.

Immunocompetent T cells are crucial in host defenses against many pathogenic fungi including Candida albicans. CD4+ T cells are essential for host defenses and the principal mechanism by which they influence host resistance is by production of cytokines. CD4+ T cells are separated into two functional categories: T helper 1 (Th1) and T helper 2 (Th2). The former produce IFN-gamma and IL-2 and are the primary mediators of host defenses associated with activation of phagocytes. Th2 cells release IL-4, IL-5, IL-10 and IL-13 that are involved in antibodies production. Another important effector mechanism is cytotoxic activity. CD8+ T cells can damage C.albicans hyphae and kill Cryptococcus neoformans directly. Another primary contribution of T cells is the production of antibodies. Also the role of natural antibody immunity in mucosal defense is
uncertain. IgA deficiency is not usually associated with C. albicans infections, nonspecific IgA enhanced adherence of C. albicans to epithelial cells, levels of vaginal IgA and IgG to C. albicans are similar in women with and without vaginal candidiasis and the presence of specific IgA in vaginal secretions did not protect against recurrent infections. However, several studies have shown that secretory IgA reduced adherence of C.albicans to epithelial cells and some antibodies can mediate protection in rat vaginal candidiasis. Vaginal vaccination with a monoclonal antibody specific for yeast killer toxin elicited a secretory IgA anti-idiotypic response which protected rats from challenge with C. albicans; passive protection was demonstrated with vaginal fluid containing antibodies to mannann constituents and the aspartyl proteinase of C. albicans. In the medical history many vaccines have been licensed for viral or bacterial diseases of humans but none have been licensed for medically important fungi. The largest clinical trial of a vaccine for a mycosis was performed by The Valley Fever Vaccine Study Group about fifteen years ago. Nearly 3000 subjects who were skin test negative for coccidioidomycosis were randomized blindly to receive either whole spherules killed with formaldehyde or saline. During five years of observation the differences in the groups, the vaccine recipients and the placebo controls, was statistically insignificant and less than 30% of vaccinated subjects manifested evidence of a response to the spherule preparation, thus it is possible that in almost 70% of subjects the vaccine was not immunogenic.

Before the approach to fungal vaccines it is important to determine what are the expectations for an effective fungal vaccine. The first goal that must be met is to create a vaccine that can limit the ability of the fungus to establish a latent state. The human host is most often successful in limiting the spread of fungal infections, but a fraction of the infection may survive for years. These niduses of infection may serve as reservoirs for reactivation if the host immune system becomes impaired. Thus any vaccine against fungi must prevent the establishment of a dormant state in the host and consequently protect against reactivation.

In recurrent vulvo-vaginal candidiasis, similarly in invasive fungal infections, there is frequently a dormant state of fungi in the host and a local vaginal immune mechanism may be responsible for the frequent relapses. Until some years ago the autogenous vaccine therapy or prophylaxis treatment with the autogenous vaccine obtained from their Candida. 64 were affected from C. albicans infection, 3 from C. parapsilosis, 2 from C. glabrata, 3 from C. krusei and 2 from C. tropicalis. The patients were women who had been suffering from at least four Candida vaginitis episodes per year for at least two years not suffering of diabetes or underwent immunosuppressive therapy. All of them had already been placed on therapy to mycotic infections several times as well as on long-term pharmacological prophylaxis. Clinical and microbiological follow-up were extended for three years after the end on the vaccination protocol. General clinical laboratory and specific immunological tests were preventively carried out periodically at the end of the treatment and every two and six months.

Materials and methods

Methods of preparation of autogenous vaccine: Vaginal discharge were cultured in agar Saboraud and the colonies of Candida present in the plate culture were isolated and identified and the fungi subcultured in Trypticase Soy Agar. After 48 hours at 37 °C the surface of medium were very gently scraped by a calibrated plastic loop and the spherules were washed three times with saline solution and resuspended in saline solution with an opacity of 1 Mc Farland. The solution so obtained were heated at 70 °C in a water bath for an hour for three days and tested for sterility. The spherules so killed were separated in four vials of 2 millilitre at the same concentration of fungi: The vials were injected in the deltoid of the patients. Selection of patients: 74 women 20-50 years old underwent the immunoprophylaxis treatment with the autogenous vaccine obtained from their Candida. 64 were affected from C. albicans infection, 3 from C. parapsilosis, 2 from C. glabrata, 3 from C. krusei and 2 from C. tropicalis. The patients were women who had been suffering from at least four Candida vaginitis episodes per year for at least two years not suffering of diabetes or underwent immunosuppressive therapy. All of them had already been placed on therapy to mycotic infections several times as well as on long-term pharmacological prophylaxis. Clinical and microbiological follow-up were extended for three years after the end on the vaccination protocol. General clinical laboratory and specific immunological tests were preventively carried out periodically at the end of the treatment and every two and six months.

Results

At the end of the treatment with
the autogenous vaccine sintonology disappeared in 62 of the patients. 6 patients reported a relevant improvement, although they still presented a modest vaginal discharge and a slight vulvar itching. The remaining six patients reported only a modest reduction in the intensity of symptoms. Laboratory follow-up in this phase showed absence of Candida in the vaginal secretion of 64 of 68 women who reported recovery or improvement; persistence of the mycetes was checked in the six patients with only modest improvement and in four subjects considered clinically recovered, one of these was affected by C. parapsylosis. It is possible consider these four patients like a colonization, a dormant state of the fungi.

One of the six women without a significant improvement was a subject with selective IgA deficiency and in two patients was not possible to have a good compliance in the regular administration of the vials. Routine hematological tests and assessment of the immunological response did not vary significantly in the general and local humoral response, particularly was not showed any variation in the levels of CD4+ and CD8+ T cells, of the seric IgG, IgA, IgM, C3 and C4 components of complement, of vaginal nonspecific IgA and of seric and vaginal specific total Igs. A significant increase of the reaction at the skin test with 0.4 ml of the same solution of the autogenous vaccine was showed in 66 patients. They showed no skin reaction before the vaccine treatment and a large reaction (1-2,5 cm of diameter) 15 days after the end of treatment. This represent the only evidence of a cell mediated immunitary response to the stimulation by the autogenous vaccine.

In the first year after the end of prophylaxis relapses occurred in 23 patients (31%), one when the patient was in the 8th week of pregnancy. In all the cases the patients related a lesser intensity of the symptoms than during the episodes before the autogenous vaccine treatment and clinical as well microbiological remission occurred without pharmacological intervention in 17 of them. A year after the end of the treatment other recurrent episodes did not occur in the patients clinically recovered. During the next two years the conditions of the patients asymptomatic, or with relevant improvement, did not vary, also in those with Candida in the vaginal secretions. In the remaining six patients without good results Candida vaginitis was detectable for all three years of observation. Collateral effects did not showed during and after the treatment except a muscular pain in the sites of injections for two or three days after.

Conclusions

Autogenous vaccines has a long medical history, they are used for treating chronic or recurrent infectious diseases and can be considered therapeutic vaccines in contrast to preventive vaccines. Autogenous vaccine sank into oblivion due to achievement in antimicrobial therapies, we think that the initial microbiological (84%) and clinical (90,5) success achieved with the autogenous vaccine in the vulvo-vaginal candidiasis are encouraging for the prosecution of the study based on the immunological approach to therapy and prophylaxis in fungal infections. Candida autovaccination to therapy and prophylaxis in recurrent vulvo-vaginal candidiasis may be an excellent alternative of the pharmacological therapy.

References

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