Journal of Cosmetics, Dermatological Sciences and Applications, 2016, 6, 191-198
http://www.scirp.org/journal/jcdsa
ISSN Online: 2161-4512
ISSN Print: 2161-4105

Tuberculin as Intralesional Therapy for Viral Warts

—Single-Blind, Split, Placebo, Controlled Study

Khalifa E. Sharquie[1,2*], Jamal R. Al-Rawi[3], Adil A. Noaimi[1,2], Wael H. Majly[4]

[1]Department of Dermatology & Venereology, College of Medicine, University of Baghdad, Baghdad, Iraq
[2]Arab Board for Dermatology & Venereology, Baghdad Teaching Hospital, Medical City, Baghdad, Iraq
[3]Department of Community Medicine, College of Medicine, Al-Mustansiriya University, Baghdad, Iraq
[4]Department of Dermatology & Venereology, Baghdad Teaching Hospital, Baghdad, Iraq
Email: *ksharquie@ymail.com, adilnoaimi@yahoo.com

How to cite this paper: Sharquie, K.E., Al-Rawi, J.R., Noaimi, A.A. and Majly, W.H. (2016) Tuberculin as Intralesional Therapy for Viral Warts. *Journal of Cosmetics, Dermatological Sciences and Applications*, **6**, 191-198.
http://dx.doi.org/10.4236/jcdsa.2016.65024

Received: June 28, 2016
Accepted: November 13, 2016
Published: November 16, 2016

Abstract

Background: BCG vaccine as an antigen has proved its effectiveness as an immunotherapy for viral warts. Tuberculin is an antigenic extract of *M. tuberculosis* capable of eliciting an immunological skin reaction. **Objective:** To assess the efficacy of tuberculin intralesional injection in the treatment of viral warts. **Patients and Methods:** This single ,blind, placebo controlled study was conducted at the Department of Dermatology, Baghdad Teaching Hospital, Baghdad, Iraq from March 2010 to July 2011.Forty-one patients with different types of viral warts were enrolled in this study; tuberculin test was done to patients prior to instillation of intralesional treatment. Then the patients treated by intralesional tuberculin in each lesion located on the right side of the body, and intralesional distilled water in each lesion located on the left side of to a maximum of 3 injections, at 2 weeks interval or until full resolution of these lesions. Patients were evaluated every 2 weeks to assess the regression of their lesions and to record any local and systemic adverse effects. The response to treatment was evaluated by decrease in size and reduction in number of warts. Scoring of response to treatment was as follow: 1) Responders: including patients who showed complete cure or those with good response (>50% reduction). 2) Non responders: including patients who showed minimal response (<50% reduction), or those with no improvement (stable disease and disease progression). The follow up period lasted up to 2 months after the last dose. **Results:** Thirty out of 41 patients had completed the study, of them 14 (46.66%) patients showed response of their lesions on the right side of the body that were treated with tuberculin; 15 patients showed no response, 1 patient showed minimal response, 7 patients showed good response and 7 patients showed complete cure (23.33%). Regarding the lesions treated with intra-

lesional distilled water, 25 patients showed no response, 3 patients showed minimal response, 2(6.66) patients showed good response and no patient showed complete cure of their warts. Of the 14 responder patients to intralesional tuberculin, 10 patients were tuberculin tested positive, and 4 patients were tested negative, and of the 16 non responder patients to intralesional tuberculin, 3 patients were tuberculin tested positive, and 13 patients were tuberculin tested negative which was statistically significant difference. No side effects reported from tuberculin therapy apart from mild pain at site of injection. **Conclusion:** Intralesional injection of tuberculin is an effective therapy for viral warts when compared with control, possibly through its local immunological action and had no systemic immunological response. Patients with previous BCG vaccine showed better response to tuberculin injection.

Keywords

Tuberculin, Intralesional Therapy, Viral Warts

1. Introduction

Viral warts are common dermatological diseases caused by different human papillomaviruses (HPVs) [1], the incidence increases during the school years to reach a peak in adolescence and early adulthood [2], Clinical manifestations depend on the HPVs type involved, anatomical location and the immune status of the host [3]. There is an increased prevalence of warts in patients with cell-mediated immune suppression [3].

A recent Iraqi study showed BCG vaccination is an effective mode of therapy for viral warts through a single, blind, placebo, controlled study and gave a cure rate of 39.7%, [4] but might cause disfiguring scar at injection site [4] and has a potential to cause serious adverse reactions especially in immune-compromised patients [5]. So the present study looking for an antigen related to BCG but free from these adverse effects like tuberculin antigen.

Tuberculin is the name given to extracts of *Mycobacterium tuberculosis* that is used in skin testing for the detection of *M. tuberculosis* infection and sensitivity. The cellular mechanisms responsible for tuberculin skin testing reactivity are related mainly to previously sensitized CD4+ T lymphocytes, which are attracted to the skin-test site, there, they proliferate and produce cytokines [6].

So the aim of the present study is to evaluate the efficacy of intralesional tuberculin in the treatment of viral warts, also to test for any systemic immune effects of intralesional tuberculin.

2. Patients and Methods

A single, blind, placebo, controlled study evaluates the efficacy and safety of tuberculin antigen; (Purified protein Derivative, PPD) in the treatment of viral warts. Forty one patients with different types of viral warts were enrolled in this study at the Department

of Dermatology and Venereology, Baghdad Teaching Hospital, Baghdad, Iraq during the period from March 2010 to July 2011. Exclusion criteria were patients with concomitant intake of immunosuppressive drugs, those who used any form of local or systemic, destructive or immunotherapeutic modalities for manipulation of their warts in the last 3 months. History and examination were carried out to determine the clinical type of the warts, size, and number of lesions, and the presence of previous BCG scar.

Tuberculin test was done to patients by injection of 0.1 ml of purified protein derivative (PPD) containing 2 tuberculin units per 0.1 ml intradermally on the volar surface of the forearm using a 27-gauge needle on a tuberculin syringe. The transverse width in millimeters of induration at the skin test site was measured after 48 - 72 hours; induration less than 5 mm was considered negative test result. Then the patients received intralesional tuberculin in each wart located on the right side of the body until the lesion get blanched, and intralesional distilled water in each wart located on the left side of the body to a maximum of 3 injections, at 2 weeks interval or until full resolution of these lesions.

The patients were evaluated and examined every 2 weeks for evidence of regression of their lesions and to record any local or systemic adverse effects. Response to treatment was evaluated by decrease in size and number of warts, and photographic comparison.

From each patient, formal consent was taken before starting therapy after full explanation about the nature of the disease, course, and the procedure of treatment, follow up, prognosis and the need for pre and post treatment photographs. Also, the ethical approval was performed by the Scientific Committee of the Scientific Council of Dermatology and Venereology-Iraqi Board for Medical Specializations. All patients were photographed by Samsung Galaxy S4 combines 13 megapixel camera.

Scoring of response to treatment:

1) Responders: including patients who showed complete cure or those with good response (>50% reduction).

2) Non responders: including patients who showed minimal response (<50% reduction), or those with no improvement (stable disease and disease progression).The follow up period lasted up to 2 months after the last dose.

3. Results

Thirty out of 41 patients had completed the trial; 14 males and 16 females. Their ages ranged from 4 - 23 years with mean ± SD 13.53 ± 5.25 years while the duration ranged from 4 - 48 months with mean ± SD 12.33 ± 8.80 months. The number of the lesions treated with intralesional tuberculin in each patient ranged from 1 - 5 with mean ± SD 2.6 ± 1.03 lesions and the number of lesions treated with intralesional distilled water in each patient ranged from 1 - 9 with mean ± SD 3.33 ± 2.022 lesions. Twenty seven patients had scar of previous BCG vaccination while 3 patients had no scar of previous BCG vaccination. Regarding the clinical variants of the lesions treated with intralesional tuberculin 26 patients had common warts including priungual and filiform

warts, 2 had plane warts and 2 had plantar warts. Regarding the clinical variants of the lesions treated with intralesional distilled water 28 patients had common warts including priungual and filiform warts, 3 had plane warts and 4 had plantar warts (5 patients had more than 1 clinical type), 13 (43.33%) patients were tuberculin tested positive and 17 (56.66%) patients were tuberculin tested negative. Regarding the lesions treated with intralesional tuberculin, 15 patients showed no response, 1 patient showed minimal response, 7 patients showed good response and 7 patients showed complete cure (23.33%). Regarding the lesions treated with intralesional distilled water, 25 patients showed no response, 3 patients showed minimal response, 2(6.66) patients showed good response and no patient showed complete cure of their warts (Table 1).

The responders to tuberculin treatment were 14 patients: 10 patients were tuberculin tested positive and 4 patients were tuberculin tested negative. In all patients and at any time of the study, the response to treatment of the lesions treated with tuberculin is superior or equal to the response of the lesions treated with distilled water. Treatment was well tolerated, and only 1 patient had pain at site treated with intralesional tuberculin that necessitates NSAIDs. No patient developed recurrence of the healed lesions during the follow up period. Two patients who failed to respond to intralesional distilled water, responded very well to intralesional tuberculin (Table 2).

4. Discussion

Viral warts are common dermatological disease, and it is now running an epidemic in Iraqi population [4], viral warts usually takes a long time even years to heal, still some

Table 1. Response rates following tuberculin intralesional injection versus intralesional distilled water.

	Tuberculin side (No. %)				Distilled water side (No. %)			
	Non-Responders		*Responders*		*Non-Responders*		*Responders*	
No of injection	*No response*	*Minim*	*Good*	*Cure*	*No response*	*Minim*	*Good*	*Cure*
Injection 1 (n = 36)	24 (66.66%)	10 (27.77%)	2 (5.55%)	0 (0%)	36 (100%)	0 (0%)	0 (0%)	0 (0%)
Injection 2 (n = 34)	17 (50%)	3 (8.82%)	13 (38.23%)	1 (2.94%)	30 (88.23%)	3 (8.82%)	1 (2.94%)	0 (0%)
Injection 3 (n = 29)	15 (51.72%)	1 (3.44%)	7 (23.33%)	7 (23.33%)	25 (83.33%)	3 (10%)	2 (6.66%)	0/30* (0%)

Chi-square = 7.19, P-value = 0.0073 Mantel Haenszel corrected-statistically significant.

*The group B patient with unhealed lesion in the left side added to the list.

Table 2. The association between tuberculin test & the response rate to therapy by intralesional tuberculin.

Response	Tuberculin		
	+ve	−ve	Total
Responder	10	4	14
Non-Responder	3	13	16
Total	13	17	30
χ^2, P-value	8.16, 0.004, Mantel Haenszel corrected-statistically significant.		

patients might not show spontaneous healing with long term follow up [1] [2]. There are many modalities of therapy and the existence of multiple treatment modalities reflects the fact that none is uniformly effective and there is no antiviraltherapy [1] Most of these modalities take months and many of them are destructive and might cause scarring, and the recurrence rate after these modalities of therapy may be high [1] [2].

The role of immunity is documented by the appearance and persistence of warts in immunosuppressed populations, and spontaneous regression of the majority of warts is related to enhanced cellular immunity [7]. Warts can disappear when the immune response is stimulated; in contrast, in persistent disorder of cell-mediated immunity the prevalence, severity of warts and the incidence of HPVs related malignancies are increased [1]. Dinitrochlorobenzene [8], interferon [9], diphencyprone [10], squaric acid dibutyl ester [11], cimetidine [12], imiquimod, [13] and intralesional injection of candida and mumps antigens [14], have been used for immunological manipulation of warts.

BCG (Bacille-Calmette-Guerin) was introduced as a prophylactic agent against tuberculosis, accidentally it has been found that leprosy incidence was decreased tremendously [15]. BCG also had been used in treatment of malignant melanoma [16], transitional cell carcinoma of bladder [17], in alopecia areata [18], and recurrent oral aphthosis [19].

BCG vaccination had been used as therapeutic remedy against viral warts and the results showed to be an effective treatment [4]. As BCG has been shown to stimulate macrophages, T and B-lymphocytes, and natural killer cell function and augment interlukin-1 production [20] and under some circumstances, specific activation of cell mediated immunity by T cell mitogen (BCG vaccine) and exposure to cytokines, particularly INF gamma may lead to enhance the nonspecific ability of activated macrophage to deal with other unrelated antigens [20]. And these were the proposed mechanisms of action.

Tuberculin (purified protein derivative) being an antigenic extract of *M. tuberculosis*, may has the same role in the treatment of viral warts and being capable of eliciting a delayed type hypersensitivity at site of injection into patients previously sensitized with tuberculosis bacilli as previously sensitized CD4+ T lymphocytes, attracted to the skin-test site. Proliferate and produce cytokines [6]. That may be of help for treatment of viral warts, with advantage over the BCG in being free from serious adverse reactions especially in immunocompromised patients [5].

In the present work Tuberculin (PPD) antigen had been used as therapeutic remedy. The response of viral warts to intralesional tuberculin injected in the lesions located on the right side of the body was statistically high when compared to response of the lesions located on the left side of the body of the same patients and treated within tralesional distilled water. And the efficacy of tuberculin intralesional injection was more confirmed by excellent response (near clearance) of lesions that were treated with intralesional tuberculin after failure of these lesions to respond to intralesional distilled water in 2 patients who showed clearance of warts treated with intralesional tuberculin

Table 3. Comparing two different modes of immunotherapy through using BCG and intralesional tuberculin injections.

BCG vaccine	Intralesional tuberculin
Using attenuated bacilli of mycobacterium.	Using antigens of mycobacterium.
Delayed immune response.	Rapid immune response.
Systemic immunological effects.	Local immunological effects.
Cure rate of 39.7% within 13 weeks.	Cure rate of 23.33% within 6 weeks.
Could be associated with many side effects like scarring, keloid formation, and disseminated infection.	No local or systemic side effects.

and no response of lesions treated with intralesional distilled water.

Most of the responders to intralesional tuberculin treatment were tuberculin tested positive, in contrast; most of the non-responder to intralesional tuberculin were tuberculin tested negative, and that may be explained by the absence of the above mentioned local reaction at site of tuberculin injection in patient not previously sensitized to *Mycobacterium tuberculosis* bacilli.

Taking in consideration that the tuberculin showed no therapeutic role on the lesions at anatomically distant area from site of injection, and the response of viral warts to intralesional DW was comparable to reported rates of spontaneous resolution [1]; so the response of viral warts to intralesional tuberculin should not be attributed to tuberculin testing that was done prior to intralesional tuberculin treatment (tuberculin test has no systemic immunomodulatory effect) [4] [7] [16] [18] [19]. Also this study had proved that intralesional injection of tuberculin had no systemic effect as the warts on the left side showed no response.

The slowly developed nature of response to therapy and the high cure rates among patients who were tuberculin tested positive may enable us to speculate that the tuberculin act by induction of local immune response rather than by direct cytotoxic effect. And the treatment was well tolerated, as no side effects were reported in any patient.

To compare the efficacy of immunotherapy through BCG vaccination and intralesional tuberculin, we conclude the followings as shown in Table 3.

5. Conclusion

Tuberculin intralesional antigen of viral warts gave encouraging results and proved as effective therapy for viral warts when compared with placebo and had no effect on distant lesions and no side effects. Also to the best of our knowledge, this is the first placebo controlled study in this regard. Further studies are needed to follow up patients for longer duration to confirm the present observation.

Disclosure

This study was an independent study and not funded by any drug companies.

References

[1] Androphy, E.J. and Lowy, D.R. (2008) Warts. In: Wolf, K., Goldsmith, L.A., Katz, S.I., Gil-

chrest, B.A., Paller, A.S. and Leffel, D.J., Eds., *Fitzpatricks Dermatology in General Medicine,* 7th Edition, McGraw-Hill Book Company, New York, 196, 1914-22.

[2] Sterling, J.C. (2010) Virus Infections. In: Burns, T., Breathnach, S., Cox, N. and Griffiths, C., Eds., *Rook's Textbook of Dermatology*, 8th Edition, Willy-Blackwell Publishing Company, Hoboken, 33, 1-81. http://dx.doi.org/10.1002/9781444317633.ch33

[3] Kirnbauer, R., Lenz, P. and Okun, M.M. (2003) Human Papillomavirus. In: Bolognia, J.L., Jorizzo, J.L. and Rapini, R.P., Eds., *Dermatology,* 1st Edition, Mosby Publishing Company, Maryland Heights, 1217-1233.

[4] Sharquie, K.E., Al-Rawi, J.R., Al-Nuaimy, A.A. and Radhy, S.H. (2008) BCG Immunotherapy of Viral Warts. *Saudi Medical Journal*, **29**, 589-593.

[5] James, W.D., Berger, T.G. and Elison, D.M. (2006) Viral Diseases. In: *Andrew's Diseases of the Skin*, *Clinical Dermatology*, 10th Edition, WB Saunders Company, Canada, 19, 403-413.

[6] Raviglione, M.C. and O'Brien, R.J. (2008) Tuberculosis. In: Fauci, A.S., Braunwald, E., Kasper, D.L., Hauser, S.L., Longo, D.L., Jameson, J.L. and Loscalzo, J., Eds., *Harrison's Principle of Internal Medicine,* 17th Edition, McGraw-Hill Company, New York, 158, 1006-1020.

[7] Majewski, S. and Jablonska, S. (1998) Immunology of HPV Infection and HPV-Associated Tumors. *International Journal of Dermatology*, **37**, 81-95. http://dx.doi.org/10.1046/j.1365-4362.1998.00435.x

[8] Naylor, M.F. (1988) Contact Immunotherapy of Resistant Warts. *J Am AcadDermato*, 19, 679. http://dx.doi.org/10.1016/S0190-9622(88)70222-4

[9] Reichman, R.C., Oakes, D. and Bonnez, W. (1990) Treatment of Condylomaacuminatum with Three Different Interferon-*α* Preparations Administered Parenterally: A Double Blind, Placebo-Controlled Trial. *The Journal of Infectious Diseases*, **162**, 1270-1276. http://dx.doi.org/10.1093/infdis/162.6.1270

[10] Buckley, D.A., Keane, F.M. and Munn, S.E. (1999) Recalcitrant Viral Warts Treated by Diphencyprone Immunotherapy. *British Journal of Dermatology*, **141**, 292-296. http://dx.doi.org/10.1046/j.1365-2133.1999.02978.x

[11] Silverberg, N.B., Lim, J.K. and Pallor, A.S. (2000) Squaric Acid Immunotherapy for Warts in Children. Journal of the American Academy of Dermatology, **42**, 803-808. http://dx.doi.org/10.1067/mjd.2000.103631

[12] Orlow, S.I. and Pallor, A. (1993) Cimitidine Therapy for Multiple Warts in Children. *Journal of the American Academy of Dermatology*, **18**, 794-796. http://dx.doi.org/10.1016/S0190-9622(09)80278-8

[13] Mario, M. (2002) Imiquimod 5% Cream: A Topical Immune Response Modifier. *International Journal of Dermatology*, **41**, 1-2. http://dx.doi.org/10.1111/j.1365-4632.2002.00016.x

[14] Johnson, S.M., Roberson, P.K. and Horn, T.D. (2001) Intralesional Injection of Mumps or Candida Skin Test Antigens: A Novel Immunotherapy for Warts. *Archives of Dermatology*, **137**, 451-455.

[15] Krogh, C.M.E. (1994) CPS Compendium of Pharmaceuticals and Specialties. 29th Edition, Canadian Pharmaceutical Association, Ottawa, 142-413.

[16] Mackie, R.M. (1992) Melanocytic Naevi and Malignant Melanoma. In: Wilkinson, A. and Ebling, F.J., Eds., Rook's *Text Book of Dermatology*, 5th Edition, Blackwell Scientific Publications, Oxford, 1525-1560.

[17] Naraynn, P. (1995) Immunology of Genitourinary Tumors. In: Macaninch, J.W. and Tanagho, E., Eds., *Smith's General Urology*, 14th Edition, Lang Medical Book, Connecticut,

234-348.

[18] Sharquie, K.E., Lafta, R.K. and Al-Sammarrai, A. (2003) BCG Immunotherapy in Patients with Alopecia Areata. *Yemeni Journal for Medical Sciences*, **3**, 1-2.

[19] Sharquie, K.E. and Hayani, R.K. (2004) BCG as a New Therapeutic and Prophylactic Agent in Patients with Severe Oral Aphthosis. *Clinical and Experimental Rheumatology*, **22**, 120.

[20] Hennessey, L.R. and Baker, J.R. (1994) Immunomodulators. In: Stites, D.P., Terr, A.L. and Parslow, T.G., Eds., *Basic and Clinical Immunology*, 8th Edition, Lange Medical Books, Stamford, 781-785.