Editorial

The trials of treating warts

Sam Gibbs

The human papilloma virus (HPV) is ubiquitous, clever, persistent and highly successful. The treatments we dermatologists have for dealing with the skin lesions caused by this virus are very numerous and, for the most part, not very sophisticated or effective. It seems reasonable to use relatively simple treatments such as topical salicylic acid for patients with only a few warts that are likely to resolve fairly soon anyway. In this situation, the physician is not exerting much of an influence on the natural history of the disease. We should have no illusions. However, patients with more widespread, refractory warts whose functional and cosmetic symptoms are very significant can make us feel uncomfortably powerless as physicians. Two clinical studies in this issue of the Journal provide some cause for cautious optimism; the avenue of immuno-manipulation may well be the most promising one to explore.

Wart treatments that are not crudely destructive and irritant but have a more sophisticated and focused effect on the immune response to HPV have attracted considerable interest over a number of decades now but progress has been slow and painstaking. In terms of mechanism of action contact sensitisers such as diphencyprone are perhaps the least focused in the immunological treatment category. Contact dermatitis in patients and those who treat them is a potential problem but the treatment is relatively simple and this approach has certainly been reported as remarkably effective with complete clearance rates of around 80%.[1-3] Further larger randomized trials of this type of treatment would definitely be welcome.

Topical imiquimod is commonly used for treating genital warts but unpublished trials carried out on common warts in 2000 by the manufacturer yielded very disappointing results (unpublished). This may be due to lack of penetration of the drug through thickened keratotic lesions. Others have reported more encouraging results[4,5] (16 of 18 children with refractory warts clearing completely and 15 of 50 adults, some immunosuppressed, with very refractory warts clearing completely, respectively). There would certainly seem to be some mileage in a drug already licensed for treating warts particularly if the cost could be reduced and penetration increased. Proper randomized trials would also be helpful.

Intralesional injections of various antigens have been of interest for some time as well but good trials again are somewhat lacking. The large randomized trial by Thomas Horn's group in the USA was unfortunately over-complicated by the introduction of a second treatment, interferon, and not very well reported.[6] A total of 57 of 95 patients (60%) injected with antigen, with or without additional interferon, experienced the resolution of at least one wart compared with 25 of 106 (24%) injected with saline or interferon alone. The number of participants who experienced complete clearance of all warts was not clearly reported, but it appeared to be 21/95 (22%) in the treatment groups and 11/106 (10%) in the 'placebo' groups. This raises an important point, namely that the loss of one distant or remote wart is of interest to the immunologist but not so much to the patient. The only outcome of any real interest to patients is permanent clearance of all warts and this is not always reflected in the way that clinical trials are reported in the medical literature. The results reported by Nofal[7] in a smaller and much simpler

Department of Dermatology, The Great Western Hospital, Marlborough Road, Swindon, SN3 6BB, UK

Address for correspondence: Dr. Sam Gibbs, Department of Dermatology, The Great Western Hospital, Marlborough Road, Swindon, SN3 6BB, United Kingdom. E-mail: sam.gibbs@gwh.nhs.uk

Access this article online

Quick Response Code:

Website: www.ijdvl.com

DOI: 10.4103/0378-6323.144142

How to cite this article: Gibbs S. The trials of treating warts. Indian J Dermatol Venereol Leprol 2014;80:495-6.

Received: June 2014. **Accepted:** September 2014. **Source of Support:** Nil. **Conflict of Interest:** None declared.

study with the use of measles, mumps, rubella (MMR) vaccine injected intralesionally (clearance of warts in 57 of 70 patients, 81%, with treatment compared with 11/40, 28%, with placebo) are much more impressive. It is not clear how the technique was so much more successful in their hands than with Horn's group but it is clear that intralesional antigen is a treatment worthy of further exploration.

What is the safest and most effective antigen and how is it best used? With this in mind, the report of Singh *et al*.[8] is of interest. In this case series, complete clearance of warts in 24 of 44 patients (54.5%) was achieved using an intralesional mycobacterial antigen. The study population was limited to immunocompetent patients with multiple warts present for at least 6 months and there appears to have been a preponderance of patients with large numbers of warts and also patients with facial warts. Case series are rather looked down upon by purists because of the lack of a control group and randomization but this type of study has the advantage of reflecting real, everyday practice, that is trying a treatment out on patients as they come along and sticking with it if it seems to work; it is a subjective and not very scientific process but what a lot of doctors do a lot of the time. A 50% success rate is approximately equivalent to what many wart treatments such as cryotherapy and salicylic acid tend to achieve for non-refactory warts in day to day practice, but if this study population truly represents a refractory subset then these results are encouraging. On the other hand, we should ask whether multiple injections with a significant risk of reactive nodules and granulomas on the shoulder or in lesions (over 80% and over 40%, respectively) is a price worth paying; although their description does not suggest it, the authors describe these as mild side effects.

The double-blind, placebo-controlled randomized trial of autoinoculation by Lal *et al*. is the study of a more unique and elaborate approach than the other techniques so far discussed. The study design is exemplary with blinding of subjects and those assessing outcome and a robust system of randomization. The report is less clear about the study population but the patients were adults referred to a tertiary centre and had to have more than five warts and most of them appear to have had their warts for at least one year. This is therefore probably a subset of patients with relatively refractory warts. The authors are at pains to report their results as a reduction in the number of warts in the whole treatment group with accompanying statistical tests but, as already pointed out, this is not an outcome that would interest individual patients and the number of warts is not the preferred unit of analysis for trials of this sort.[10] In this trial, complete cure occurred in 15 of 24 (62.5%) of the treatment group and none of the placebo group. Assuming we are dealing with refractory warts, this is, again, an encouraging result but not one of strikingly impressive effectiveness. In addition, the technique would appear to be quite labor intensive requiring three somewhat complicated surgical treatments and a modest risk of pigmentary change and keloid scarring. Again, is it worth it? Is there any way this approach could be modified to make it simpler or safer?

Warts are very troublesome, and it is also troublesome trying to treat them and trying to sort out how to treat them. Each new trial and each new variation on the theme of immuno-manipulation edges us a little closer to a treatment that might one day be as clever and effective as the virus itself.

REFERENCES

1. Rosado-Cancino MA, Ruiz-Maldonado R, Tamayo L, Laterza AM. Treatment of multiple and stubborn warts in children with 1-chloro-2,4-dinitrobenzene (DNCB) and placebo. Dermatologia Revista Mexicana 1989;33:245-52.
2. Wilson P. Immunotherapy vs cryotherapy for hand warts; a controlled trial (abstract). Scottish Med J 1983;28:191.
3. Buckley DA, Keane FM, Munn SE, Fuller LC, Higgins EM, Du Vivier AW. Recalcitrant viral warts treated by diphencyprone immunotherapy. B J Dermatol 1999:141:292-6.
4. Grussendorf-Conen EI, Jacobs S. Efficacy of imiquimod 5% cream in the treatment of recalcitrant warts in children. Pediatr Dermatol 2002;19:263-6.
5. Hengge UR, Esser S, Schultewolter T, Behrendt C, Meyer T, Stockfleth E, *et al*. Self-administered topical 5% imiquimod for the treatment of common warts and molluscum contagiosum. Br J Dermatol 2000;143:1026-31.
6. Horn TD, Johnson SM, Helm RM, Roberson PK. Intralesional immunotherapy of warts with mumps, Candida, and Trichophyton skin test antigens: A single-blinded, randomized, and controlled trial. Arch Dermatol 2005;141:589-94.
7. Nofal A, Nofal E. Intralesional immunotherapy of common warts: Successful treatment with mumps, measles and rubella vaccine. J Eur Acad Dermatol Venereol 2010;24:1166-70.
8. Singh S, Chouhan K, Gupta S. Intralesional immunotherapy with killed *Mycobacterium indicus pranii* vaccine for the treatment of extensive cutaneous warts. Indian J Dermatol Venereol Leprol 2014;80:509-14.
9. Lal NR, Sil A, Gayen T, Bandyopadhyay D, Das NK. Safety and effectiveness of autoinoculation therapy in cutaneous warts: A double - blind, randomized,placebo - controlled study. Indian J Dermatol Venereol Leprol 2014;80:515-20.
10. Altman DG, Bland JM. Statistics notes. Units of analysis. BMJ 1997;314:1874.