Immunomodulating Activity of Cimetidine in Iraqi Children and Adolescents with Common Warts

Hussein Abbas Alsultany Ifad Kerim Alshibly
College of Medicine, Babylon University, Hilla, Iraq.

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Abstract:

Back ground and objectives: Warts are epithelial proliferations on the skin and mucous membrane caused by various types of human papilloma viruses. Wart lesions can decrease spontaneously or increase in number and size according to patient's immune status. Many modalities of treatments have been used but none of them proved to be uniformly effective. Cimetidine has important effects on the immune system and are used as immunomodulator in the treatment of various skin diseases. This study was designed to evaluate the therapeutic effectiveness and immunomodulatory activity of cimetidine among children and adolescents with multiple recalcitrant common warts.

Materials and methods: Sixty eight patients (37 female and 31 male, 3-18 years old) diagnosed with multiple recalcitrant common warts were the subject of the study during the period from February 2013 to the end of December 2013. All patients were treated with cimetidine (40mg\kg\day) in two divided doses for three months duration. Monthly visits were conducted to observe size and number of the warts and side effects of the medication. Serum levels of IL-12, γ-INF, and TNF-α were measured by ELISA technique during each of the three months duration of cimetidine therapy.

Results: The therapeutic response to high dose regime of cimetidine among the 62 patients who completed the study revealed that, 48 patients (77.5%) had either significant clinical improvement or complete resolution of their wart lesions after the third month of the study course. While immunological study analysis demonstrated that there was a significant (P=0.05) increment in serum levels of IL-12, TNF-α and γ-IFN after three months regime of cimetidine therapy.

Conclusions: Through its immunomodulating activity, cimetidine can be proven to offer a safe and very effective treatment option against multiple recalcitrant common warts in children and adolscents.

Key words: Warts, Cimetidine, IL-12, TNF-α and γ-IFN.

الخلاصة:

الثآليل هي نمو طلائي في الجلد والأغشية المخاطية الناجمة عن مختلف أنواع فيروسات الورم الحليمي البشري(HPV). تؤلول الآفات يمكنه الإنقاص أو الزيادة في العدد والحجم وفقا للحالة المناعية للمريض. وقد استخدمت العديد من طرائق العلاج لكن أيا منها لم تثبت أن تكون فعالة على نحو موحد. عقار السيميتيدين له آثار هامة على الجهاز المناعي، وتستخدم هذه الأنواع من الأدوية المتلاعبة بالجهاز المناعي في علاج الأمراض الجلدية المختلفة. صممت هذه الدراسة لتقييم الفعالية العلاجية وخاصية المفعول التلاعبي المناعي للسيميتيدين ضد البثور بين الأطفال والمراهقين المصابين بالبثور الجلدية المعاندة المتعددة.

ثمانية و ستين من المرضى (٣٧ من الإناث و ٣١ من الذكور،في عمر ٣–١٨ سنة) تم تشخيصهم بالثآليل الجلدية المعاندة المتعددة خلال الفترة من شباط/فبراير ٢٠١٣ إلى نهاية كانون الأول/ديسمبر عام ٢٠١٣. جميع المرضى أعطوا علاج السيميتيدين (40mg\kg\day) في جرعات مقسمة اثنتين لمدة ثلاثة أشهر. وأجريت زيارات شهرية لمراقبة حجم وعدد البثور والآثار الجانبية للدواء. وقيست مستويات المصل IL–12, TNF–α, INF– γ بتقنية ELISA خلال كل شهر لمدة ثلاثة أشهر من فترة علاج السيميتيدين. النتائج كشفت الاستجابة العلاجية لنظام جرعة عالية من السيميتيدين بين المرضى الذين أكملوا الدراسة وهم٦٢، ٤٨ مريضا (٧٧.٥%)

قد تحسنوا سريريا بصورة شبه كاملة من هذه الآفات البثرة بعد الشهر الثالث من مدة الدراسة. في حين أظهر تحليل الدراسة المناعية أنه كان هناك ارتفاع إحصائي ملحوظ كبير (P = 0.05) للزيادة في مستويات المصل IL-12, TNF-α, INF- γ بعد ثلاثة أشهر من الدراسة.

Introduction:

Warts are benign intraepidermal neoplasms that are caused by human papilloma viruses (HPVs), a double-stranded DNA papovavirus that commonly affect children and adolescents[1]. There are more than 150 types of HPVs have been identified and are associated with various skin diseases. In warts, HPV enters the host through a break in the epidermis, and autoinoculation is common[2]. HPV infection is spread by direct contact from one child to another within the nearby children and from one area to another in a child on the same youngster[3]. The incubation time is variable, ranging from few weeks to more than one year[4]. The prevalence of warts in the general population is unknown, the estimated peak incidence is 3-20%, occurring mostly between the ages of 9 and 16 years[5].

Clinically, the four most common types of cutaneous warts are the common wart (verruca vulgaris), plantar wart (verruca plantaris), flat wart (verruca plana), and genital wart (condyloma acuminatum) [5]. Common warts typically occur on humans' hands or feet but less often in other locations[1]. Although these lesions rarely pose a serious health problem, spontaneous cure may occur, but it takes much time, yet some patients might not show this spontaneous healing[6], resulting in further physical impairment and psychosocial discomfort[2].

Warts may progress spontaneously or increase in number and size according to the immune status of the patient[5]. Cell-mediated immunity is required to keep the infection in check, as demonstrated by the high prevalence of warts among immunosuppressed organ-transplant recipients and patients with acquired immunodeficiency syndrome [7]. In chronic viral disease such as warts, there is a shift from Th1 (cellular immunity) to the Th2 (humoral immunity). Since antibodies are not as effective in defeating viruses as are the cells themselves, viral diseases progress when humoral immunity is dominated [8].

Th1 cell types is enhanced by cytokines such as Interleukin-2 (IL-2), Interleukin 12 (IL-12), and gamma interferon (γ-IFN)[9]. The inflammatory cytokines IL-12, and INF-γ, and tumor necrosis factor-alpha (TNF-α) modify and enhance the immune response in many skin diseases, including cutaneous warts[10]. IL-12 stimulates Killer T cells in the mucus membranes to stop viral invasions before they get enter the body[8]. Interferons (IFNs) belong to a family of proteins involved in the regulation and function of the immune system and are important in both innate and specific immune responses against viruses, specifically IFN-γ, plays a key role in the innate immune response[11]. On the other side, natural killer cells(NK cells), the primary source of TNF-α are frontline troops in defense against HPV infections[12].

Conventional methods of treatment nonspecifically destroy infected tissue. These methods include cryosurgery; excision; carbon dioxide or pulsed dye laser ablation; and destructive chemical agents such as salicylic acid[13]. They are painful and can be very scary to children, often require multiple sessions[2], resulting in poor compliance, cosmetic disfiguration, and residual indolent lesions usually leading to incomplete treatment[14]. Nevertheless, many of these treatment

modalities are nonspecific or require multiple visits to the practitioner[15], even some may require general anesthesia[16].

Because wart proliferation is controlled by the immune system, various methods have been tried to stimulate an immune response to HPV but none is uniformly effective or directly antiviral[7,17]. Immuno-modulating agents are less painful than the traditional destructive therapies and thus more easily tolerated by children. However, their efficacy has yet to be thoroughly demonstrated[1]. One such agent, cimetidine (tagamet)^{R}, is a histamine H_2 receptor antagonist that is approved by the FDA for reduction of the secretion of gastric acid[18]. Though, in high doses, it is thought to act as an immunomodulatory agent by enhancing the cell-mediated immune response[2].

Dermatological uses of cimetidine has been reported in the literature in recent years, however with conflicting results[14]. The immune response induced by cimetidine has been beneficial for many types of viral skin infections[10]. Administration of cimetidine increases proliferation of lymphocytes and inhibits the function of suppresser T cells[5]. It enhances cellular immunity[19], increases the activity of natural killer cells[12], increases mitogen-induced lymphocyte proliferation[13], and interferes with the functioning of suppressors T-lymphocytes through its H_2 receptors, so it contributes significantly to the functioning of the immune system[20].

Children with multiple recalcitrant common warts remain a unique population in whom effective, safe and painless treatment would be advantageous. So, it looks feasibly to define cimetidine therapeutic efficacy and its immunodulatory activity among local Iraqi children and adolescents complaining from multiple recalcitrant common warts.

Materials and methods:

This is an opened therapeutic trial study design. Sixty eight patients (37 female and 31 male) diagnosed with multiple recalcitrant common warts who intended the private clinic and dermatological outpatient clinic in Merjan Medical Teaching Hospital, Hilla, Iraq were the subject of the study during the period from February 2013 to the end of December 2013. Their age ranged 3–18 years (mean age 13 years). All patients were examined clinically to assess the number and location of the lesions, then interviewed and detailed questionnaires were completed for each of them. The nature of the disease, course, prognosis, and full information related to the cimetidine therapy including the possible side effects, action, and way of intake were explained to the patients and to their parents. Oral consent was taken from the parents prior to their children's inclusion in this study.

Patients were selected according to the following inclusion criteria: presence of ten or more, recalcitrant cutaneous warts, that is, patients who had been submitted to two or more treatment approaches by destructive methods without resolution of clinical presentation; patients whose last treatment course had finished at least two months before the study started; absence of chronic diseases, commitment not to use other drugs during treatment.

The questionnaire contained a full history for each patient regarding the name, age, sex, occupation, marital status, duration of disease, family history of warts, past medical history (states of immune suppression, organ transplantation or any chronic diseases), drugs history especially for corticosteroids and other immune suppressants or any previous treatment modality received for their warts. Physical examination was performed for

each patient to assess the number, presence of other types of warts, the examination was aided by taking several photos for each patient using the same digital camera (Sony /cyber shot) from approximately the same view and distance. The numbers of lesions were calculated.

Serum levels of INF-γ ,TNF-α and IL-12 were measured using ELISA technique (enzyme amplified sensitivity immunoassay (EASIA) kits, BioSource Europe SA, 8 B-1400, Nivelles, Belgium). The BioSource kits are a solid phase sandwich enzyme linked immunosorbent assay. The absorbance of each well was read at 450 nm within 2 hours after adding the stop solution. The absorbance of the standards was plotted on graph paper against the standard concentration to construct the standard curve.

All patients were treated with cimetidine (40mg\kg\day) in two divided doses for three months. After prescribing Cimetidine, review was performed monthly, observing size and number of the warts and side effects of Cimetidine, beside the serum level of the studied cytokines .

Clinically the response to treatment was graded as follows:

0= no response

1= mild response (1-25% reduction in lesion no.)

2= moderate response (26-50% reduction in lesion no.)

3= significant response (51-75% reduction in lesion no.)

4= excellent response (76-100% reduction in lesion no.)[22]

If complete response occurred at the end of second or third month, patients were followed up monthly for 4 months to detect any recurrent lesions or persistent side effects, the follow-up is performed by monthly visits. If at the end of third month, no or mild response occurred, the patients were instructed to continue using the same dose of cimetidine for another month and then they were reevaluated at the end of fourth month; then if response occurred, the patients were followed up for 4 months as mentioned above, but if no response occurred, they were considered as treatment failure.

Statistical analysis:

Statistical analysis of all results were preceded by the help of SPSS version 15 software statistical package using P value at level of significance less than 0.05.

Results:

During the period from February to December 2013, a total of 68 patients with multiple recalcitrant common warts were included in this study. Only 62 patients completed the study (six patients were regarded as defaulters and excluded from the study). Age and gender distribution results were illustrated in the table(1).

Table (1) Age and Gender Distribution

Age intervals	Total no.(%)/♀:♂
<5 years	4(6%)/1:1
5-10 years	20(29.5%)/1.22:1
10-15 years	28(41%)/1.15:1
15-20 years	16(23.5%)/1.3:1
Mean age/years	13
Total no./%	68(100%)/1.19:1

At the end of each of the three months of 40mg/kg/day cimetidine therapy, sixty two patients with multiple recalcitrant common warts were examined to determine the efficacy of treatment.

After one month of treatment, the cure rates were obtained, there were 9 patients (14.5%) who got no response, mildly responding patients were 6 forming 9.6%, while moderately responding patients were 17 forming 27.5%. On the other side there were 19 patients who got significant and 11 patients who got excellent response both forming 48.5% (30.5% and 17.5% respectively) out of the 62 patients who intended and completed the first month of the study.

The response rate to cimetidine therapy was elevated after the second month of treatment. One of the non-responders got response thus lowering the overall no-response rate to 12.9%, the mildly responding patients became lesser (only 3) and lowering their rate to 4.8%, while 8 patients were moderately responding formed 17.5%. Twenty five patients got significant response so elevating their rate to 40.5%, while 15 patients had excellent response forming 24% out of 62 patients.

Finally at the end of third month, response rate increased as shown in table (2). Only 5 patients remain as non-responders forming 8% out of the total number of patients. One patient had mild response forming 1.5%, 8 patients got moderate response forming 13%. On the other side 28 patients were significantly cured, and 20 patients got excellent response both forming 77.5% out of all the 62 patients who completed the study. (P=0.05).

Table (2) Response to Cimetidine Therapy

No. of patients / Response type	After 1 month/%	After 2 months/%	After 3 months/%
No response	9/14.5%	8/12.9%	5/8%
Mild response	6/9.6%	3/4.8%	1/1.5%
Moderate response	17/27.5%	11/17.5%	8/12.9%
Significant response	19/30.5%	25/40.5%	28/45%
Excellent response	11/17.5%	15/24%	20/32.5%
Total no.	62	62	62

The reported adverse side effects by the patients during the treatment course with cimetidine included nausea, epigastralgia and pruritus, as shown in the table (3), results demonstrated that almost all patients remain free of unendurable side effects which necessitating cessation of therapy. The most frequently recorded side effect was nausea (5 patients), followed by pruritus (2 patients), while only one patient had epigastralgia after three months of cimetidine therapy(P=0.05).

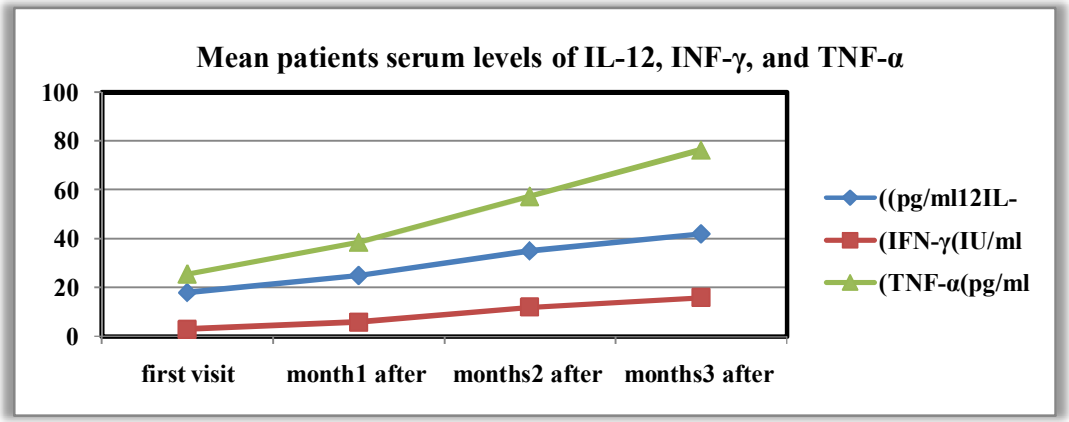
Table (3) Side Effect of Cimetidine Treatment

Side effect	No. of patients after 1 month(%)	No. of patients after 2 months(%)	No. of patients after 3 months(%)
No side effects	55(88.7%)	52(83.8%)	54(87%)
Nausea	4(6.5%)	6(9.5%)	5(8%)

Pruritus	**3(4.5%)**	**4(6.5%)**	**2(3%)**
Epigastralgia	**0(0%)**	**0(0%)**	**1(1.5%)**
Total no.	**62(100%)**	**62(100%)**	**62(100%)**

Serum Levels of IL-12, TNF-α and γ-IFN were determined by an enzyme-linked immune-sorbent assay (ELISA). Levels were measured at the first time of inclusion to the study, then at the monthly visits for three consecutive months. The average baseline readings of the studied cytokines was 18 pg/ml for IL-12, 3 IU/ml for INF-γ, and 25.6 pg/ml for TNF-α. These levels increased significantly thereafter through the second month.

Results obtained after the third month of treatment course with 40mg\kg\day cimetidine therapy showed that there was a significant increment (P=0.05) in the mean serum level of these cytokines as that, the mean serum level of IL-12 increased to 42 pg/ml, INF-γ level increased to 16 IU/ml, while serum level of TNF-α reached 76.4 pg/ml as illustrated in figure (1).



Figure(1) Serum Levels of the Cytokines

Discussion:

Warts are the reason for nearly one-fifth of all pediatric visits for dermatological clinics. Especially in children, warts continue to pose a therapeutic challenge[3].

This study is an open labeled therapeutic trial, made by attribution of sixty eight patients complaining from multiple recalcitrant cutaneous warts aged 3-18 years attended the private clinic and the outpatient clinic of dermatology in Merjan Medical Teaching Hospital, Hilla Province, Iraq from the period from February to the end of December 2013.

The first studied factor was the age and gender distribution of warts, data from the collected questionnaire illustrated in table(1) showed that, among the different age groups been included in the study the highest compliance from cutaneous warts was observed in the age intervals of 10-15 years. Most affected patients were those children and adolescents at school age forming 70.5% of all the study population (41% from 10-15 years and 29.5% from 5-10 years), this age distribution may reflect the period of maximal exposure as warts are contagious disease and exposure among school chums is highly expected. Taking into consideration that warts may take place at any age, it is more common in children and adolescents[2]. This high frequency of acquiring warts at this specific age group that we found came in line with another author[21],

who announced that the incidence of cutaneous warts increases in the school years to reach its peak between the age 12 and 16 years, then declines sharply, and more gradually thereafter. These findings were supplemented by the fact that, up to 15 percent of children will be affected by these unsightly skin lesions before the age of ten[3].

Treatment of warts in children is difficult, may be painful using traditional methods, especially if they are multiple or on the face[22], so it is desirous to have an effective and painless treatment that shows rapid results[4]. This study was conducted to determine the safety and efficacy of three months regime of 40mg/kg/day cimetidine therapy in a group of 68 local Iraqi children and adolescent with multiple recalcitrant common warts. The therapeutic response to high dose regime of cimetidine among the 62 patients who completed the study period revealed that, 48 patients (77.5%) had either significant clinical improvement or complete resolution of their wart lesions after 3 months of 40mg/kg/day cimetidine therapy(P=0.05), of them no patient demonstrated disease progression while receiving the medication and complete responders remained free of lesions at 4 months period of follow-up. While for those patients who showed mild-moderate response (9 patients (14.5%)), another month of therapy was encouraged, two of them had significant response with 75% reduction in their warts number or size. None of the non-responders showed enhanced cure even after additional month with high dosage therapy.

Most therapies take a long time to work, some are ineffective, and others are painful[21]. Even when the treatment seems to work and the wart is cured, there is no guarantee that it will not return[3]. In children, spontaneous regression of warts may occur but some may never be cured spontaneously and still present some new lesions during follow up[5]. Results about the use of cimetidine in warts treatment have been conflicting, a lot of authors encourage it [12,14,16,23,24,25], while some discourage it [1,5] especially in adults, yet others recommend its use as a second line therapy in combination with another drugs[15].

The role of cimetidine in children is more an open question. Cimetidine might still have a role in the treatment of warts in children, justifying its use against multiple recalcitrant common warts [19]. Taking into consideration that efficacy of cimetidine is not satisfactory regarding its use for adult warts, a trend toward its efficacy is suggested for younger subjects[23].

Through this study in order to investigate the safety of cimetidine therapy in children, the adverse reactions had been looked for at monthly visits, as shown in table(3), it was noticed that, the most frequently reported side effect was nausea (8%), followed by pruritus(3%), while only 1.5% of patients got epigastralgias after three months of cimetidine therapy. Those side effects were somewhat tolerable ones as they did not necessitate the suspension of cimetidine therapy. It is known that the incidence of adverse reactions in cimetidine is low and normally minimum, below 3%. In one study, the most frequent adverse events from the use of cimetidine were nausea, epigastralgia, and diffuse pruritus, but these were attenuated by dividing the total dose and taking the pills with the meals[5].

Warts are caused by the human papilloma virus (HPV), which does not induce inflammatory cytokines; therefore, therapeutic options aimed at modulating the immune system and facilitating the production of cytokines have been proposed[1]. Cimetidine is

postulated to act as an immunomodulating agent at high doses by inhibiting suppressor T-cell function while increasing lymphocyte proliferation, thereby enhancing cell-mediated immune responses[4]. The paradigm between Th2 cells, and Th1 cells predominance is reflected in the level of cytokines they secret. Hence in order to verify the hypothesis that Th1 cells type is dominated in cases with effective treatment, so serum IL-12, TNF-α and γ-IFN would be elevated in this cohort of patients we measured concentrations of these cytokines in serum samples for all the study participants results showed that there was a significant (P=0.05) increment in the serum levels of IL-12, TNF-α and γ-IFN after three months regime of cimetidine therapy. Thus, the measurement of serum cytokines may allow for better monitoring and prediction of disease severity and therapy effectiveness, a property that could make them possible candidate biomarkers in determining wart prognosis and response to cimetidine therapy. As a consequence, we confirmed by some other authors[5], believe that complete remission did not depend on number of warts, but it reflects the immune status of the host. Cimetidine activates Th1 cells to produce IL-2, IL-12, TNF-α and IFN-γ and that their expression correlates with good cellular immunity and wart remission[18]. Another role for cimetidine is to stimulate T-lymphocyte populations, which are important in controlling viral infections[26]. So, at high dosages cimetidine could be considered for use in children who cannot tolerate destructive treatment methods[7]. Patients who received cimetidine were shown to exhibit enhanced cell-mediated immunity, restoration of sensitivity following development of acquired tolerance, and increased responses of lymphocytes to mitogen stimulation[20].

At last, it is clear that as cimetidine is regarded as immune response modifier. It has shown us the importance of cytokines, and the innate immune system in fighting a multitude of skin diseases, and more over the potential benefits of immune response modification have the ability to change the way we deliver health care.

Conclusions:

Since many conventional "destructive" treatments for warts are painful, expensive, and may cause scarring, cimetidine may offer a safe and very effective treatment alternative.

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