Available online at www.sciencedirect.com
SCIENCE DIRECT
ELSEVIER
177
JNMU
Journal of Nanjing Medical University, 2009, 23(3):177-182
www.elsevier.com/locate/jnmu
Research Paper

Clinical observations on the treatment of infantile hemangiomas with topical imiquimod 5% cream ☆

Zhengtuan Guo[a], Guowei Li[b,*], Quan Xu[a], Ya Gao[a], Peng Li[a], Xiansheng Zhang[a], Yitao Duan[a], Xinkui Guo[a], Baijun Zheng[a]

[a]*Department of Pediatric Surgery, the Second Affiliated Hospital of Medical College of Xi' an Jiaotong University, Xi' an 710004, China;*
[b]*Department of General Surgery, the Second Affiliated Hospital of Medical College of Xi' an Jiaotong University, Xi' an 710004, China*

Received 3 March 2009

Abstract

Objective: To observe the efficacy and safety of topical imiquimod 5% cream in the treatment of uncomplicated infantile hemangiomas (IHs). **Methods:** A total of 68 IHs were treated with topical imiquimod 5% cream. Among them, 36 were superficial, 22 were mixed, and 10 were deep. The size of IHs ranged from 1.0 cm × 1.5 cm to an area of a whole forearm. All the hemangiomas were in a proliferative stage. Imiquimod was applied 3 times weekly in 44 patients and 5 times weekly in 24 patients for up to 36 weeks. **Results:** All superficial IHs improved, and 18 achieved complete clinical resolution, 10 had excellent improvement, 5 showed moderate improvements, and 3 patients displayed minimal improvement. Two mixed IHs showed excellent improvement, 3 showed moderate improvement and 5 manifested minimal improvements. The remaining 12 mixed IHs and all deep IHs did not respond to the therapy. The total incidence of local adverse events was 58.82%(40/68), which included erythema or edema, local itching, incrustation or peeling, erosion or ulceration, although most of these were mild to moderate reactions and did not affect the treatment. Scarring occurred in 2 mixed IHs. No systemic side effects developed. **Conclusion:** Imiquimod 5% cream may be a safe and effective alternative for the treatment of superficial IHs and some mixed IHs in which the superficial component predominates. An appropriate treatment duration for proliferative IHs treated with this therapy may be 24 weeks. Some local adverse events, such as crusting and erosion with possible scarring potential may occur and should be addressed by prompt, but temporary, discontinuation of the imiquimod. Topical imiquimod 5% cream can be prudently used in the treatment of IHs larger than 5.0 cm×5.0 cm in newborns and infants less than 6 months of age. To our knowledge, this is the largest IH group treated with imiquimod that has been reported in the literature to date.

Keywords: infantile hemangioma; imiquimod; treatment

INTRODUCTION

Infantile hemangiomas(IHs) are one of the most common vascular tumors of childhood. Although most are benign in their behavior and involute spontaneously, they often cause extreme parental distress, and complications may lead to considerable morbidity and permanent disfigurement, depending on their location and size[1]. Current treatment options include observation for spontaneous remission, topical, intralesional and systemic corticosteroids, interferon, chemotherapeutics, cryosurgery, radiation, embolization, surgery and laser therapy[1-3]. However the potential side effects or invasive consequences, and cosmetic problems in neonates and infants are problematic. Recently, several reports suggested the potential therapeutic role of imiquimod 5% cream in the management of IHs, but the small-sample size of these studies limits the interpretation of their results[4-8]. We report our experience here with 68 proliferating IHs treated with imiquimod 5% cream during a two year period.

☆ This work was supported by Science and Technology Foundation of shaanxi Province(2005K13-G6).
*Corresponding author
E-mail address: Liguowei 1964@sina.com

PATIENTS and METHODS

Patient selection

Between May 2005 and June 2007, patients with IH who were referred to the Department of Pediatric Surgery of The Second Hospital of Medical School of Xi'an Jiaotong University were selected for the study. IHs were diagnosed clinically using the ISSVA's (International Society for the Study of Vascular Anomalies 1996) criteria, and the patients were no more than six months of age. The largest size of IHs which could tolerate the therapy was based on the patient's reaction. Exclusion criteria were: (i)complicated IH which had to be rapidly controlled, such as an eyelid IH; (ii)presence of more than one lesion at presentation; (iii)IH previously or currently treated with other methods; (iv) history of another disease with any local or systemic treatment known to have any effect on IH; (v)presence of any contraindication to local treatment, such as ulceration, bleeding or infection. The study was approved by the Research Ethics Committee of this Hospital. A detailed explanation of the natural history of IH and the nature of the study was given to the parents. If the subjects agreed with the conditions, informed consent was obtained.

Methods

Imiquimod 5% cream(Li Ke Jie, Hu Bei Keyi Pharmaceutic Co, Ltd, China) was rubbed into the clean, dry, IH-area at bedtime, without occlusion until it disappeared. The area was washed with neutral soap and warm water 6~8 hours after application. The frequency of application was three to five times per week. The amount of cream used per application was based on the size of IH and related literature[4-10]. The maximum duration of treatment was limited to 36 weeks. The patients were seen every 2 weeks and were evaluated for therapeutic response, tolerability, and adverse effects. If inflammation and/or crusting developed, the medication was temporarily discontinued. Data collection included demographic characteristics, age of onset of the IH, physical examination, and response to therapy. Photographs and measurements of the lesions were done at each visit.

Clinical evaluations

The primary outcome endpoint was the proportion of lesions which resolved with treatment. The response to treatment was evaluated as follows(refer to Oliverio's criteria[5]): Clinical Resolution-complete disappearance of the lesion; Excellent Improvement-75% to 99% decrease in the size of the lesion; Moderate Improvement-50% to 74% decrease in the size of the lesion; Minimal Improvement-25% to 49% decrease in the size of the lesion; Failure- < 25% decrease in the size of the lesion.

Secondary outcome variables included the incidence of local or systemic side effects or complications.

Statistical analysis

Descriptive statistics were used to summarize the patients'demographic characteristics(age, sex) and the background characteristics(age at treatment, treatment frequency, duration of treatment). For the purpose of statistical analysis, the IHs were stratified into three groups: superfcial, mixed and deep, to determine whether the superficial IHs responded better than the mixed and deep IHs. The χ^2 test was used to compare the treatment failure rate and complication rate among the three groups. Correlation analysis was used to evaluate the relationship between the curative effects and the sizes of lesions. $P < 0.05$(two-tailed) was considered to be statistically significant.

RESULTS

A total of 68 infants, 50 girls and 18 boys, with an average age of 14 weeks(range: 2.4-27 weeks) were included. In all, 36 IHs were superficial, 22 mixed, and 10 deep. The sizes of IHs ranged from 1.0 cm×1.5 cm to an area of a whole forearm and were larger than 5.0 cm × 5.0cm in 18 patients, which was the maximal size in published reports[4-8]. All patients were treated during the proliferative phase. ***Table 1*** showed the anatomical location of the lesions.

Table 1 **Anatomical location of the lesions**

Anatomical location	N
Head and neck	30
Scalp	13
Face	7
Neck	10
Trunk	17
Extremity	21
Total	68

Imiquimod 5% cream was initially applied 3 times a week in all patients. The frequency was increased to 5 times a week in 24 patients after 4 weeks of treatment, when no clinical improvement was observed. The mean duration of treatment was 24 weeks(16-36 weeks).

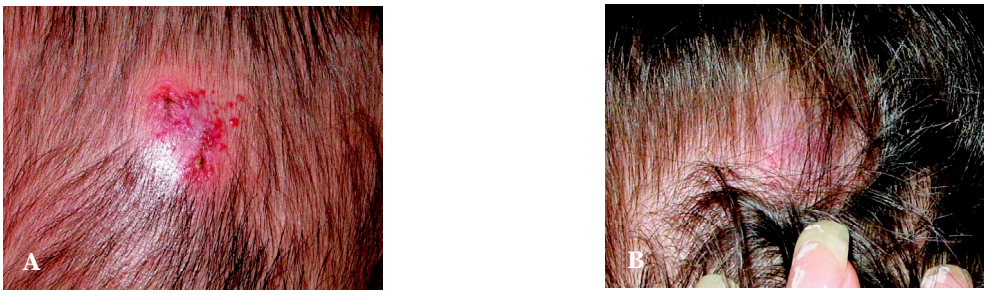
All superficial IHs improved. Of these, 18 achieved complete clinical resolution(***Fig. 1***), 10 had excellent improvement(***Fig. 2***), 5 showed moderate improvements, and 3 patients displayed minimal improvement. Progressive changes in the color of the lesion from red to dusky red were also observed. Of all the mixed HIs, 2 showed excellent improvement(***Fig. 3***), 3 showed moderate improvement and 5 manifested minimal improvement. The remaining 12 lesions and all deep IHs did not respond to therapy. The curative effects in the three groups were summarized in ***Table 2***. The differences in treat-ment failure rates between the three groups were

statis-tically significant(χ^2 =43.08, P< 0.005). There was no correlation between the curative effects and the sizes of lesions in this patient population(r = 0.067, P > 0.50). Most improved lesions first showed arrest of growth in 4 to 8 weeks, and then a reduction in size and depth in color began, with significant responses mostly occurring in 16 to 36 weeks(mean 24 weeks) after treatment. There was no evidence of recurrence in all improved lesions at a median of 3 months following the last treatment.

Table 2 **Curative effects in three groups**

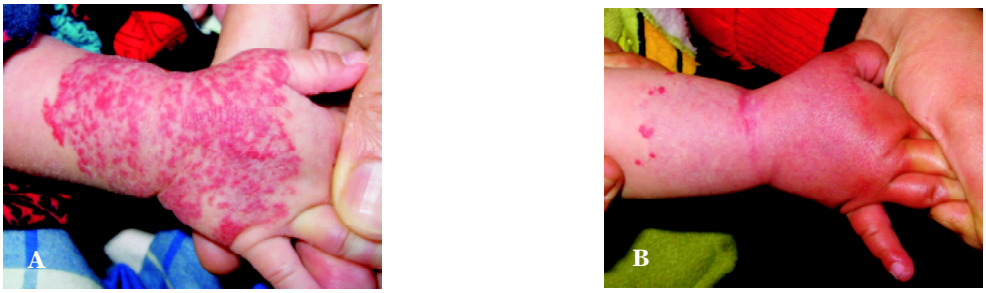
	Resolution	Excellent	Moderate	Minimal	Failure	Total
Superficial	18	10	5	3	-	36
Mixed	-	2	3	5	12	22
Deep	-	-	-	-	10	10
Total	18	12	8	8	22	68

χ^2=43.08, P < 0.005(comparison of treatment failure rate among the three groups).



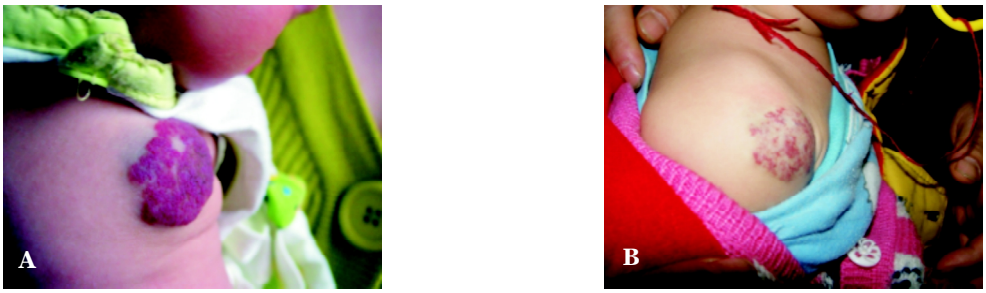
(A) Before treatment; (B) after 24 weeks of treatment.

Fig. 1 A girl, 12 weeks after birth, with a superficial IH on the scalp, classified as clinical resolution after 24 weeks of treatment



(A) Before treatment; (B) after 28 weeks of treatment, showing almost clinical resolution with dermathemia, and only a few red spots remaining.

Fig. 2 A boy, 5 weeks after birth, with a large superficial IH involved area of right forearm, wrist and back of hand, classified as excellent improvement with 28 weeks of treatment



(A) Before treatment, (B) after 20 weeks of treatment.

Fig. 3 A girl, aged 24 weeks, with a mixed IH on the right shoulder, classified as excellent improvement with 20 weeks of treatment

Local adverse effects or complications occurred in 40 of all the IHs cases(58.82%). These included erythema or/and edema, local itching, incrustation or peeling, erosion or ulceration, and scarring. Two or more of these symptoms or adverse events could happen in one lesion. ***Table 3*** showed the distribution of patients with local side effects or complications. The incidences of local adverse effects in the three groups were similar and there were no statistically significant difference between groups(χ^2 =0.01, P> 0.05)(***Table 4***). Most local side effects were mild to moderated reactions and did not affect the treatment. Scarring developed in 2 mixed IHs because of incrustation and ulceration respectively, which has not previously been reported. No systemic side effects were observed in any of the patients.

Table 3 **Distribution of patients with local side effects or complications**

local side effects or complications	N
Erythema or Edema	20
Incrustation or Peeling	13
Erosion or Ulceration	11
Local itching	19
Scarring	2
Pigment anomaly	0
Total	*40

*Some patients had two or more side effects

Table 4 **Distribution of patients with local side effects or complications in the three IH groups**

local side effects or complications	Superficial *n*=36	Mixed *n*=22	Deep *n*=10
Erythema or Edema	11	6	3
Incrustation or Peeling	7	4	2
Erosion or Ulceration	6	4	1
Local itching	10	6	3
Scarring	0	2	0
Pigment anomaly	0	0	0
Total	*21	*13	*6

*Some patients had two or more side effects

$x^2=0.01, P < 0.005$(comparison of incidences of local adverse effects among the three groups).

DISCUSSION

In 1994, topical treatment of IHs was first reported by Elsas and Lewis who reported on 5 patients with vision-threatening periocular capillary hemangiomas that were treated with topical clobetasol propionate (glucocorticoids) cream, and 2 patients received steroid eye drops. All experienced a decrease in the size of their IHs[11]. Later, Cruz and colleagues also demonstrated that topical clobetasol propionate cream improved three vision-threatening eyelid IHs. It seemed that this topical treatment modality provided an additional alternative for managing superficial IHs[12]. Recently, 34 infants with proliferating hemangiomas of infancy who were treated with ultrapotent topical steroids were reviewed retrospectively[13]. In this series, IHs in 74% of the infants demonstrated either good or partial response to treatment with ultrapotent topical corticosteroids. Of the responders, the majority reported cessation of the lesion growth expected for their age. Improvement varied, with thinner superficial hemangiomas demonstrating better cosmetic improvement than thicker lesions. However, there were still some potential side effects, such as skin atrophy or systemic adverse effects from percutaneous absorption of the steroid hormones[11-13].

Imiquimod, an imidazoquinoline amine, is a novel synthetic topical immune-response modifier which is capable of inducing a number of cytokines, including interferon(IFN) alpha, interleukin(IL)-6 and tumor necrosis factor alpha(TNF-α. Other immune modulators may also be induced including IL-1, IL-5, IL-8, IL-10, and IL-12, cytotoxic T lymphocytes, and IFN-gamma[14]. In addition, it was demonstrated experimentally that imiquimod can inhibit the growth of induced hemangioendotheliomas in a mouse model. This inhibition was associated with increased expression of tissue inhibitor of matrix metalloproteinase-1(TIMP-1) and decreased activity of MMP-9[15], and an increase in apoptosis[16]. These findings were also seen in hemangiomas undergoing spontaneous involution[17]. Imiquimod has been shown to be effective in the treatment of many kinds of cutaneous tumors and viral infectious diseases, such as superficial basal cell carcinoma[18], squamous cell carcinoma in situ[19], malignant melanoma[20], pyogenic granuloma[21], genital warts[22], molluscum contagiosum[23], actinic keratoses[24], and even some cutaneous tumors in immunocompromised patients[25].

Imiquimod 5% cream was first reported to be successful in two patients with IHs in 2002[4]. Up to now, there have been 5 reports of a total of 36 patients with IHs who have received topical treatment with imiquimod 5% cream and the preliminary results have been satisfactory, with few side effects. However, all these studies had small samples that limit the interpretation of results[4-8].

The outcome of our study showed that the efficacy of topical imiquimod 5% cream in the treatment of IHs was closely related to the depth and thickness of the lesions, but not related to the lesion surface area. Superficial hemangiomas are mainly located in the superficial dermis, and are raised, lobulated, and bright red. All 36 superficial IHs improved, and of these 18 achieved complete clinical resolution, 10 had excellent improvement, 5 showed moderate improvements, and 3 patients displayed minimal improvement, and a progressive change in the color of the lesion from red to dusky red was observed. These responses are similar to those reported in a recent retrospective study[7]. The clinical manifestations of mixed IHs are complicated. In a study by Ho and colleagues, all 3 mixed IHs showed only a little improvement[7]. In contrast, in our study the improvement was excellent in 2 of 22 mixed IHs, 3 showed moderate improvement, and 5 manifested minimal improvement. In all these mixed HIs the color change and reduction of tumor size was similar to that seen in superficial lesions, while the remaining 12 mixed IHs and all deep IHs did not respond to therapy. We analyzed the improved mixed IHs further and found that the majority of these lesions were superficial, so the contact area with imiquimod 5% cream was larger, probably

accounting for the fact that they showed improvement. The mixed IHs, in which the majority of the lesions were deep, and all deep IHs did not respond to the therapy. This may have been due to the smaller contact area or lack of contact of the lesion with the imiquimod. During therapy, we observed that the superficial component shrank and deep component grew in some mixed HIs. These facts suggested that the percutaneous action of imiquimod is only limited to the superficial area, and does not reach deeper regions. During the course of treatment, we did not find any lesions in this group that completely disappeared in a short time, such as 16 weeks, as has been described by other authors[4-8]. This might be attributed to the fact that the average age of patients in our study was younger than that in those reports[4-8], and the IHs were perhaps proliferating more rapidly. We noticed that the growth of a proliferative IH was controlled in 4 to 8 weeks, and then the lesion began to be reduced in area, depth and color. Significant responses mostly occurred in 16 to 36 weeks(mean 24 weeks) after treatment. Although 16 weeks is a standard course of treatment in cutaneous viral infectious diseases, we recommend that imiquimod 5% cream should be administered for at least 24 weeks in the treatment of proliferative IHs in patients aged less than 6 months.

Local adverse events developed in 40 IHs in this study, which mainly presented as inflammatory reactions, including erythema, edema, local itching, incrustation, peeling, erosion and ulceration. Although most of these were mild to moderate reactions and did not affect the treatment, scarring was observed in 2 patients with mixed His. This scarring occurred in one case of incrustation and one of ulceration respectively, and has not previously been reported. Some authors presume that the action of imiquimod in enhancing immunity might translate in an expected inflammation, generally considered as the required reaction associated with a clinical response[4-6,15], and should not, therefore, be interpreted as a real adverse effect[5]. However, more than a half of the IHs in our study, in which we achieved complete clearance or excellent improvement, did not exhibit any inflammation. It seemed that a local inflammatory reaction was not essential for the imiquimod curative effect.

Crusting and erosion with the potential of possible scarring should be of concern, especially in treating IHs located in areas predisposed to constant friction. Prompt discontinuation of imiquimod and administration of a topical antibiotic minimized permanent sequelae. Local itching was an important issue, which could cause scratching in older infants, and lead to ulceration and infection, and perhaps scarring, especially in patients with mixed HIs. In such cases, nail cutting was necessary. We also found that the incidence of local adverse effects was not related to the depth of the lesions, which suggested that the adverse effects were the result of interaction of drug and skin, but not the interaction of drug and tumor.

Studies on pharmacokinetics and safety in adults with actinic keratoses[9] and children with molluscum contagiosum aged 2-12 years[10] showed that percutaneous absorption of imiquimod cream was minimal, and safety margins for topical imiquimod were broad. There are no similar studies in infants. The dosage of topical imiquimod 5% cream in the treatment of many skin diseases in young children is mainly based on the practitioners' experience. The maximum size of IH treated with topical imiquimod 5% cream in known reports was no more than 5.0 cm × 5.0 cm, because of the uncertainty of adverse systemic events[4-8]. Transient fever has been reported in two infants with IHs treated with topical imiquimod 5% cream, which did not show a dose response[8]. When we applied topical imiquimod 5% cream to larger IHs in this study, the 3 largest lesion even involving a whole forearm, the results were satisfactory and there were no systemic side effects. Although there are no studies on pharmacokinetics and safety in infants and newborns, our experience suggested that topical imiquimod 5% cream can be cautiously introduced in the treatment of some larger IHs(> 5.0 cm × 5.0 cm) in newborns and infants aged less than 6 months. Our experience suggests that this can be done even before pharmacokinetic and placebo-controlled prospective studies are conducted to ascertain the safety and efficacy of imiquimod 5% cream in this age group.

References

[1] Bruckner AL, Frieden IJ. Hemangiomas of infancy. *J Am Acad Dermatol* 2003; 48(4): 477-93.

[2] Musumeci ML, Schlecht K, Perrotta R, Schwartz RA, Micali G. Management of cutaneous hemangiomas in pediatric patients. *Cutis* 2008; 81(4): 315-22.

[3] Ranchod TM, Frieden IJ, Fredrick DR. Corticosteroid treatment of periorbital haemangioma of infancy: a review of the evidence. *Br J Ophthalmol* 2005; 89(9): 1134-8.

[4] Martinez MI, Sanchez-Carpintero I, North PE, Mihm MC Jr. Infantile hemangioma: clinical resolution with 5% imiquimod cream. *Arch Dermatol* 2002; 138(7): 881-4; discussion 884.

[5] Welsh O, Olazaran Z, Gomez M, Salas J, Berman B. Treatment of infantile hemangiomas with short-term application of imiquimod 5% cream. *J Am Acad Dermatol* 2004; 51(4): 639-42.

[6] Hazen PG, Carney JF, Engstrom CW, Turgeon KL, Reep MD, Tanphaichitr A. Proliferating hemangioma of infancy: successful treatment with topical 5% imiquimod cream. *Pediatr Dermatol* 2005; 22(3): 254-6.

[7] Ho NT, Lansang P, Pope E. Topical imiquimod in the treatment of infantile hemangiomas: a retrospective study. *J Am Acad Dermatol* 2007; 56(1): 63-8.

[8] Barry RB, Hughes BR, Cook LJ. Involution of infantile haemangiomas after imiquimod 5% cream. *Clin Exp Dermatol* 2008; 33(4): 446-9.

[9] Harrison LI, Skinner SL, Marbury TC, Owens ML, Kurup S, McKane S, *et al.* Pharmacokinetics and safety of imiquimod 5% cream in the treatment of actinic keratoses of the face, scalp, or hands and arms. *Arch Dermatol* Res 2004; 296(1): 6-11.

[10] Myhre PE, Levy ML, Eichenfield LF, Kolb VB, Fielder SL, Meng TC. Pharmacokinetics and safety of imiquimod 5% cream in the treatment of molluscum contagiosum in children. *Pediatr Dermatol* 2008; 25(1): 88-95.

[11] Elsas FJ, Lewis AR. Topical treatment of periocular capillary hemangioma. *J Pediatr Ophthalmol Strabismus* 1994;31(3): 153-6.

[12] Cruz OA, Zarnegar SR, Myers SE. Treatment of periocular capillary hemangioma with topical clobetasol propionate. *Ophthalmology* 1995; 102(12): 2012-5.

[13] Garzon MC, Lucky AW, Hawrot A, Frieden IJ. Ultrapotent topical corticosteroid treatment of hemangiomas of infancy. *J Am Acad Dermatol* 2005; 52(2): 281-6.

[14] Sauder DN. Immunomodulatory and pharmacologic properties of imiquimod. *J Am Acad Dermatol* 2000; 43(1 Pt 2): S6-11.

[15] Sidbury R, Neuschler N, Neuschler E, Sun P, Wang XQ, Miller R, *et al.* Topically applied imiquimod inhibits vascular tumor growth in vivo. *J Invest Dermatol* 2003; 121(5): 1205-9.

[16] Razon MJ, Kraling BM, Mulliken JB, Bischoff J. Increased apoptosis coincides with onset of involution in infantile hemangioma. *Microcirculation* 1998; 5(2-3): 189-95.

[17] Takahashi K, Mulliken JB, Kozakewich HP, Rogers RA, Folkman J, Ezekowitz RA. Cellular markers that distinguish the phases of hemangioma during infancy and childhood. *J Clin Invest* 1994; 93(6): 2357-64.

[18] Beutner KR, Geisse JK, Helman D, Fox TL, Ginkel A, Owens ML. Therapeutic response of basal cell carcinoma to the immune response modifier imiquimod 5% cream. *J Am Acad Dermatol* 1999; 41(6): 1002-7.

[19] Patel GK, Goodwin R, Chawla M, Laidler P, Price PE, Finlay AY, *et al.* Imiquimod 5% cream monotherapy for cutaneous squamous cell carcinoma in situ(Bowens'disease):a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2006; 54(6): 1025-32.

[20] Ray CM, Kluk M, Grin CM, Grant-Kels JM. Successful treatment of malignant melanoma in situ with topical 5% imiquimod cream. *Int J Dermatol* 2005; 44(5): 428-34.

[21] Ezzell TI, Fromowitz JS, Ramos-Caro FA. Recurrent pyogenic granuloma treated with topical imiquimod. *J Am Acad Dermatol* 2006; 54(5 Suppl): S244-5.

[22] Beutner KR, Spruance SL, Hougham AJ, Fox TL, Owens ML, Douglas JM Jr. Treatment of genital warts with an immune-response modifier(imiquimod). *J Am Acad Dermatol* 1998; 38 (2 Pt 1): 230-9.

[23] Bayerl C, Feller G, Goerdt S. Experience in treating molluscum contagiosum in children with imiquimod 5% cream. *Br J Dermatol* 2003; 149 Suppl 66: 25-9.

[24] Tran H, Chen K, Shumack S. Summary of actinic keratosis studies with imiquimod 5% cream. *Br J Dermatol* 2003; 149 Suppl 66: 37-9.

[25] Johnson R, Stockfleth E. Imiquimod 5% cream for the treatment of cutaneous lesions in immunocompromised patients. *Acta Derm Venereol Suppl(Stockh)* 2003; (214): 23-7.