Manejo de las Queratosis actínicas
Revision basada en la evidencia monitoreado por DynaMed Systematic Literature Surveillance.
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Treatment overview:

- avoid sun exposure, use sunscreen
- observation acceptable if few superficial lesions, treat if increase in size, induration or failure to regress within 1 year
- nodular lesions should be biopsied (shave or excisional) unless < 0.5 cm
- most common treatment is cryotherapy - may produce hypopigmentation in dark-skinned individuals
- other mechanical methods are excision, electrodesication and curettage, chemical peels and laser resurfacing
- insufficient long-term evidence comparing management strategies for actinic keratoses
    - systematic review of 45 articles relevant to actinic keratoses
    - no studies reported on quality of life, morbidity, mortality or incidence of squamous cell carcinoma
    - treatments shown to reduce visible actinic kertoses by 75% to 80% over 3-4 months include
        - 5-fluorouracil
        - photodynamic therapy
        - medium depth chemical peel with trichloroacetic acid
    - cryosurgery associated with 1.2% recurrence rate in cohort of 70 patients with 1,018 lesions followed for 1-8.5 years
    - 5-fluorouracil therapy associated with 25% rate of new or recurrent actinic keratoses at 2 years and 50% at 3 years
    - Reference - AHRQ evidence report from OHSU Evidence-Based Practice Center 2001 May 19 PDF

Medications:

- medications (topical) for actinic keratosis
    - aminolevulinic acid (ALA, Levulan Kerastick) 20% solution $108.02, requires photoactivating blue light (BLU-U) for 1,000 seconds on next day (cost not included)
    - diclofenac 3% gel (Solaraze) twice daily for 60-90 days $105.00
    - fluorouracil (5-FU) twice daily for 2-4 weeks
        - 2% solution in generic $51.40 or Efudex $69.70
        - 5% solution in generic $74.50 or Efudex $102.90
        - 5% cream in Efudex $102.25
        - 1% cream (Fluoroplex) twice daily for 2-6 weeks $80.40
        - 0.5% cream (Carac) once daily for maximum 4 weeks $98.10
    - imiquimod 5% cream (Aldara) twice weekly for 16 weeks $518.76
    - Reference - The Medical Letter 2004 May 24;46(1183):42
- topical 5-fluorouracil (Efudex) twice daily
    - will be red and sore in 2-4 weeks

- will crust and peel - then stop medication
- healing in 1-2 months
- side effects - reddening, itching, burning, pain or soreness, tenderness, scaling, swelling
- thicker lesions may evolve into squamous cell carcinoma
- combination with tretinoin enhances effectiveness - shorter treatment, intensive tissue reaction, more discomfort
- pretreatment with tretinoin 1-3 months may reduce treatment time with 5-FU
- pretreatment (3 days prior) with cryotherapy, 5-FU reduces likelihood of hypopigmentation
- some suggest concomitant use of topical steroids to avoid inflammation, avoid steroids in ulcerated or eroded areas (delays healing)
- cool compresses for 20 minutes for pain relief
- guideline for 5-FU treatment
  - face - 1-2% 5-FU for 3 weeks, 3-5 days to appearance of inflammation
  - face - 5% 5-FU for 2-2.5 weeks, 2-3 days to appearance of inflammation
  - scalp, neck - 5% 5-FU for 4 weeks, 4-7 days to appearance of inflammation
  - hands, arms - 5% 5-FU for 6-8 weeks, 10-14 days to appearance of inflammation
  - back, chest - 5% 5-FU for 4-6 weeks, 10-14 days to appearance of inflammation
  - Reference - J Am Acad Derm 1981 Jun;4(6):633
- fluorouracil 0.5% (Carac) cream is formulation with 0.35% in microspheres FDA approved for multiple actinic or solar keratoses on face and anterior scalp; apply once daily up to 4 weeks, may apply sunscreen or moisturizer 2 hours later; avoid exposure to sun or UV light; should not be used in dihydrodipyrimidine dehydrogenase deficiency which may cause abdominal pain, bloody diarrhea, vomiting, fever, chills (Monthly Prescribing Reference 2001 Mar;A-16)
- **fluorouracil 0.5% cream once daily effective**, based on 2 randomized 1-4 week trials with 384 patients with at least 5 actinic keratoses > 4 mm; total clearance of actinic keratoses occurred in 1.6% placebo patients, 20% using fluorouracil for 1 week, 28.7% for 2 weeks and 52.9% for 4 weeks; study funded by drug manufacturer (J Am Geriatr Soc 2001 Apr;49(4):S83,P224); 65% placebo cream users had irritation, mostly mild; 92-96.5% fluorouracil cream users had irritation which was severe in 3.5% 1-week group, 32% 2-week group and 42% 4-week group (J Am Geriatr Soc 2001 Apr;49(4):S84,P227)
- **topical fluorouracil once daily for 1 week modestly improves clearance rates (level 1 [likely reliable] evidence)**
  - 144 patients with 5 or more actinic keratoses on face were randomized to topical 0.5% fluorouracil vs. vehicle once daily for 7 days with residual lesions treated with cryosurgery at 4 weeks, 136 (94%) followed up at 6 months
  - at 4 weeks, mean actinic keratosis lesion count reduced by 62.4% vs. 28.8% ($p < 0.001$) and 16.7% vs. 0 had complete clearance ($p < 0.001$, NNT 6)
  - at 6 months, mean actinic keratosis lesion count reduced by 67% vs. 45.6% ($p = 0.01$) and 30% vs. 7.7% had complete clearance ($p < 0.001$, NNT 5), 6-month results based on interim analysis of 12-month trial
  - 18% vs. 4% had skin irritation ($p = 0.02$, NNH 7), 14% vs. 14% had eye irritation
  - Reference - Arch Dermatol 2004 Jul;140(7):813

- tretinoin (Retin-A) 0.05% once daily, 0.025% for sensitive skin, wait 2-4 months for failure of response
- topical tretinoin 0.1% cream for 4 months reduced number and size of actinic keratoses in randomized trial, but > 90% had retinoid dermatitis (JAMA 1988 Jan 22-29;259(4):527); retinol (metabolized to retinoic acid) may cause less erythema but has not been studied for efficacy, retinol predates Dietary Supplement Health and Education Act of 1994 so can be marketed without proof of efficacy and safety (Alternative Medicine Alert 2001 Nov;4(11):127)
- application of 5% lidocaine can greatly reduce discomfort especially in actinic cheilitis
- topical diclofenac

    - diclofenac sodium 3% (Solaraze) 3% gel twice daily for 60-90 days FDA approved for treatment of actinic keratoses; efficacy determined in 3 vehicle-controlled trials with 427 adults with at least 5 actinic keratoses; comparing diclofenac vs. vehicle for outcome of complete clearing of lesions 30 days after treatment, 34-47% vs. 18-19% achieved this outcome after 90-day treatment, 31% vs. 10% after 60-day treatment and 14% vs. 4% after 30-day treatment; contraindicated if aspirin allergy or third trimester of pregnancy, avoid sunlight, minimize use of other NSAIDs since some absorption occurs (Monthly Prescribing Reference 2002 Jan;A-10)
    - Solaraze appears better tolerated than topical fluorouracil (Efudex) but less effective (Prescriber's Letter 2002 Feb;9(2);11)
    - diclofenac 3% in hyaluronic acid 2.5% gel 1 g twice daily to actinic keratosis up to 180 days shows promise as first-line topical therapy (Arch Dermatol 1997 Oct;133(10):1239 in Am Fam Physician 1998 Apr 15;57(8):1956)
- imiquimod cream 5% (Aldara) twice per week for 16 weeks (e.g. every Monday and Thursday)
    - apply before sleep, wash off after 8 hours with soap and water, do not use more than one 250-mg single-use packet per treatment
    - imiquimod (Aldara) FDA approved for actinic keratoses on face or scalp, produces apoptosis in malignant but not normal human keratinocytes (The Medical Letter 2004 May 24;46(1183):42)
    - commentator notes that although short-term efficacy of imiquimod is similar to 5-fluorouracil, imiquimod takes 8 times longer (J Watch Online 2005 May 13)
    - **imiquimod improved clearing compared to placebo**
        - 492 adults with 4-8 actinic keratoses within 25 cm2 area on face or scalp were randomized to imiquimod 5% vs. vehicle alone 3 times per week for 16 weeks; at 2 months after treatment, 48% vs. 7% had complete clearance (NNT 2.4), 64% vs. 14% had partial clearance (NNT 2); 41% had local side effects and 9% required discontinuation due to side effects; complete clearance occurred in none of patients without erythema and 65% with severe erythema (Arch Dermatol 2005 Apr;141(4):467 in J Watch Online 2005 May 13)
        - 436 patients with 4-8 actinic keratoses on face or scalp within 25 cm2 area were randomized to imiquimod 5% vs. vehicle alone 2 times per week for 16 weeks in 2 trials; at 8 weeks after treatment, 59% vs. 12% had 75% or greater reduction in lesions (NNT 2.1), 45% vs. 3% had complete clinical clearing (NNT 2.4), 18% vs. 2% had severe erythema (NNH 6.5) (J Am Acad Dermatol 2004 May;50(5):714), commentary can be found in Evidence-Based Medicine 2005 Jan-Feb;10(1):11
        - 39 patients with 5-15 actinic keratoses in 1 facial area were randomized to imiquimod 5% vs. vehicle alone 3 times per week for 3 weeks (with course repeated 4 weeks later if < 75% clearance); 72% vs. 30% had at least 75% clearance of lesions (NNT 2.4) (Australas J Dermatol 2003 Nov;44(4):250)
    - imiquimod (Aldara) cream 3x/week at night for up to 12 weeks (reduce to 1-2x/night if severe skin irritation) had 84% complete clearance rates (compared to none with placebo) in 12-week randomized trial of 36 patients with multiple actinic keratoses (Arch Dermatol 2002 Nov;138(11):1498 in Prescriber's Letter 2003 Jan;10(1):4); adverse effects included severe erythema in 80%, severe erosions in 40%, severe flaking or ulceration in 20-30% (Am Fam Physician 2003 May 1;67(9):1986), commentary can be found in POEMs in J Fam Pract 2003 Mar;52(3):184
    - adverse effects include
        - erythema, flaking and scabbing in nearly all patients
        - edema, erosions or ulcers in half
        - some patients develop vesicles
        - more severe reactions associated with greater lesion clearing
        - Reference - The Medical Letter 2004 May 24;46(1183):42

    - imiquimod may cause systemic effects through diffusion of cytokines from skin into systemic circulation; fatigue, influenza-like illness, exfoliative dermatitis, and angioedema have been reported; systemic effects related to frequency of dosing (The Medical Letter 2004 Nov 8;46(1195):92)
- photodynamic therapy
    - **topical aminolevulinic acid (ALA) photodynamic therapy appears highly effective (level 2 [mid-level] evidence)**; 243 patients with multiple actinic keratoses (mostly 4-7) of face and scalp randomized to ALA vs. placebo followed within 14-18 hours by photodynamic therapy, retreatment at 8 weeks if remaining lesions (30% patients); follow-up of 211 (87%) at 8 weeks and 201 (83%) at 12 weeks, response rates with 75% or more lesions cleared were 77% vs. 18% at 8 weeks (NNT 2) and 89% vs. 13% at 12 weeks (NNT 2), intention to treat analysis not reported (Arch Dermatol 2004 Jan;140(1):41 in JAMA 2004 Apr 21;291(15):1815)
    - single treatment with photodynamic therapy had similar efficacy as 3 weeks of 5-fluorouracil in small trial; 17 patients with actinic keratoses on backs of hands had right and left hands randomized to 5-FU (topical 5-FU twice daily for 3 weeks) vs. PDT (topical 5-aminolevulinic acid then irradiation 4 hours later with specialized light source), 14 patients (82%) completed study at 24 weeks, mean reduction in lesional area 70% vs. 73% (difference not statistically significant) (J Am Acad Dermatol 1999 Sep;41(3 Pt 1):414 in JAMA 1999 Nov 17;282(19):1800h); study design does not rule out contralateral treatment effects, e.g. immunogenic responses (DynaMed commentary)
    - amino-levulinic acid topical solution 20% (Levulan Kerastick) FDA approved for use with photodynamic therapy for nonhyperkeratotic actinic keratoses of face or scalp (Monthly Prescribing Reference 2000 Mar;A-24)
    - BLU-U Blue Light Photodynamic Therapy Illuminatory FDA approved for treatment of nonhyperkeratotic actinic keratoses of face and scalp, used with aminolevulinic acid in Levulan PDT system (Am Fam Physician 2001 May 15;63(10):2071)
    - guidelines for topical photodynamic therapy from British Association of Dermatologists can be found in Br J Dermatol 2002 Apr;146(4):552 PDF or at National Guideline Clearinghouse 2005 Aug 15:6622

Surgery:

- excision or cryotherapy (topical liquid nitrogen) if benign biopsy
- review of electrosurgery of skin lesions can be found in Am Fam Physician 2002 Oct 1;66(7):1259, correction can be found in Am Fam Physician 2002 Dec 15;66(12):2208

Other management:

- review of cryosurgery for common skin conditions can be found in Am Fam Physician 2004 May 15;69(10):2365, commentary can be found in Am Fam Physician 2005 Aug 15;72(4):573
- **carbon dioxide laser resurfacing, 30% trichloroacetic acid peel, and 5% fluorouracil cream appear to have similar efficacy (level 2 [mid-level] evidence)**
    - based on small randomized trial with non-randomized control group
    - 27 patients with history of facial or scalp actinic keratoses or basal or squamous cell carcinoma were randomized to carbon dioxide laser resurfacing vs. 30% trichloroacetic acid peel vs. 5% fluorouracil cream twice daily for 3 weeks
    - 5 of 7 patients who refused study treatment were used as controls
    - all 3 treatments associated with 83-92% reduction in actinic keratoses at 3 months ($p = 0.03$)
    - all 3 treatments associated with lower incidence of nonmelanoma skin cancer over 4 years ($p < 0.001$)

    - no significant differences comparing treatment groups
    - Reference - Arch Dermatol 2006 Aug;142(8):976

Prevention and Screening

Prevention:

- avoid sun exposure
- use sunscreen
    - regular use of sunscreens prevented actinic keratoses in controlled trials of 6 months and 2 years (N Engl J Med 1993 Oct 14;329(16):1147, Arch Dermatol 1995 Feb;131(2):170 in The Medical Letter 1999 May 7;41(1052):43)
    - **daily sunscreen application but not beta carotene supplementation may reduce development of actinic keratoses**; 1,621 Australians 25-74 years old randomized to daily sunscreen use vs. usual sunscreen use and randomized to beta-carotene 30 mg vs. placebo PO once daily from 1992 to 1996; ratio of actinic keratoses in 1994 relative to 1992 was 1.2 with daily vs. 1.57 with usual sunscreen use, reduction in 1996 was not statistically significant, beta carotene had no effect (Arch Dermatol 2003 Apr;139(4):451)

References including Reviews and Guidelines

Reviews:

- review of skin cancer can be found in Am Fam Physician 2000 Jul 15;62(2):357

Patient Information

Patient information:

- handout from EBSCO Publishing Health Library PDF or in Spanish PDF
- handout from Patient UK
- handout on sun exposure can be found in Am Fam Physician 2000 Jul 15;62(2):375
- handout on men and sun exposure can be found in Am Fam Physician 2000 Jul 15;62(2):381