Spironolactone Treatment of Late Onset Acne in Adult Women

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Introduction:

Acne is one of the commonest dermatologic problem. Untreated acne may be source of physical and psychological problem. Acne is mainly seen in young persons but also affect adults.

There has been considerable advances in acne therapy. Despite these advances treatment failure with systemic antibiotic is becoming a global problem [1] and the failure of acne to respond may reach 82% in patient with post adolescent acne [2]. In a retrospective study 79% of adult women with late onset acne failed to respond to antibiotics. In two studies, treatment failure with isotretinion has been reported to be 32% and 16% respectively [2,3]. These results revealed the need to have an alternative affective treatment. The hormonal aspect of acne are of importance in treating adult woman with acne, hirsutism, and androgenic alopecia [4].

There is growing evidence that anti-androgen therapy can correct Seborrhoea, acne, hirsutism and hair loss in women [5,6].

To achieve successful treatment of such androgen excess disorders with anti androgen and hormonal treatment the physician must have a good knowledge of such drugs.

The drugs may act at many levels including hypothalamus, pituitary gland, adrenal glands, gonads and target cells in the skin [7].

The androgen receptors blockers which are the most oftenly used antiandrogens in dermatology include [7]:

1. Spironolactone
2. Flutamide.
3. Cyproterone acetate.

Other drugs that reduced androgen expression include:

4. Oral Contraceptives.
5. Gonadotrophin releasing harmone agonists.
6. Inhibitors of 5 á reductase.
7. Corticosteroids.

1. <u>Spironolactone</u> is one of the most effective therapies [5].

Basically, Spironolactone has been used to treat essential hypertension, congestive heart-failure, ascitis of hepatic origin and primary hyperaldosteronism [8].

Spironolactone a synthetic steroid with structural resemblance to aldosterone [9]. It acts as aldosterone antagonist and competes with aldosterone receptors in the distal nephron to produce natriuresis, potassium retention, diuresis and reduction of blood pressure [8].

Spironolacton acts as an anti androgen by :

a. Altering steroidogeneses in adrenal and gonadal tissue.
b. Affecting target organ response to circulating androgens and acts as androgen receptor blocker and has been used to treat acne and hirsutism in women [10,7,11,12].
c. Increased androgen catabolism with increased conversion of testesterone to eostradiol.

Spironolactone selectively destroys microssomal Cytochrome P-450 in testes and adrenal glands[13] leadings to decreased activity of androgenic enzymes and decreased steroidogenesis[13] in experimental animals with 60 – 75% reduction in plasma testesterone[14].

In humanbeings, oral Spironolactone administration results in variable effects on serum level of androgens[15,16,17]. When Spironolactone is taken by mouth, 70 % of the dose is absorbed by gastrointestinal tract [18]. The Spironolactone is metabolized in the liver and is changed into its active from Canrenone [19], whose half life is 4 – 8 hours [14], while the half life of Spironolactone in serum is only 10 minutes [20]. Other studies showed that the half life of the Spironolactone is 1.4 hour, and metabolized in liver first to 7-alfa thiospironolactone with half life 13.8 hours and later to – Canrenone with half life of 16.5 hours [21,22].

Spironolactone competitively blocks cytosol receptors for dihydrotestesterone at target organ within the hair follicle [12].

Spironolactone can be used in low doses as a single drug or as an adjuvant to standard acne therapy in women with adult onset acne with favorable outcome and tolerance and improve oily skin and hirsutism [23].

It is recommended to start with low doses of Spironolactone 25 – 50 mg per day. The effective dose range from 25 – 100 mg per day and response to treatment may require 1 – 3 months in acne, and up to 6 months in hirsutism [21,22].

5% Spironolactone cream was used topically to treat Seborrhoeic acne in males and females for one month with complete – regression in 30%, and improvement in 65% and the topical preparation was well tolerated without systemic side effects [24,25,26].

Systemic Spironolactone is used successfully to treat oily skin, acne, hirsutism and androgenic alopecia in women.

Adverse reactions in ladies is confusion, lethargy, nausea, vomiting, diarrhoea and menstrual irregularity[27,28]. Patients may get metrorrhagia, abnormal bleeding between menses and this may necessetate lowering the dose of Spironolactone. Potassium retention may occur and patient may get low blood pressure.

Concomitant use of contraceptive pills with Spironolactone minimize hormonal side effects [29,27].

Spironolactone use in human beings does not appear to cause malignancy as proved by animal experiments over 25 years [30], and as shown from multiple human epidemiologic studies and metabolic studies [31]. The recommended dose of Spironolactone to treat acne in adult women is 100 – 200 mg per day [32,29,33]. In a retrospective study of 85 patients treated with Spironolactone [3], 73 patients were evaluated with the following results:

1. 33% were cured, with no acne or with occasional isolated lesions.
2. Other 33% improved, and showed more than 50% improvement.
3. 27.4 % demonstrated partial improvement, with less than 50% improvement, and only 5 patients out of 73 failed to respond to Spironolactone.

In the same study, the side effects to the use of Spironolactone were:

1. 17.5 % reported menstrual irregularity.
2. 16.3 % reported lethargy, fatigue, dizzeness or headache.
3. 13.7 % has light hyperkalemia
4. Blood pressure was recorded before and after treatment in 19 patients and there was 15 mm Hg reduction in Systolic pressure, and 10 mm Hg in diastolic pressure with a mean reduction of 5 mm Hg systolic and 2.6 mm Hg diastolic.
5. Fewer than 5% reported symptoms as breast tenderness, increased diuresis, postural light headedness, nausea, and decreased libido.

In the same study [3] beneficial side effects were reported as:

1. Improved symptoms of premenstrual syndrome 16.2%.
2. Improvement of facial seborrhoea in 11.2 %.
3. Decreased metrorrhagea 2.5 %.
4. Reduced endometriosis pain in 1.2 %.
5. Increased libido in 1.2 %.

2. <u>Flutamide</u> is a nonsteroidal androgen receptor blocker used primarily to treat metastatic prostate carcinoma. It is less potent as androgen receptor blocker than Spironolactone. It is used to treat women with acne, hirsutism and androgenic alopecia.

Several studies showed improvement of hirsutism and clearance of acne [6,34,35].

Flutamide is well absorbed from gastro-intestinal tract and is rapidly metabolized to the active metabolite hydroxyflutamide with half life 5– 6 hours and is excreted in urine. The dose in men for prostatic cancer is 750 mg per day. The dose in females is 375 mg per day. It causes sever gastro-intestinal side effects such as nausea gastric distress and increased appetite.

The main side effect is liver toxicity which occurs in 1 % of men [36,37].

The starting does is usually 125 mg per day. Flutamide in combination with contraceptive pills was used to treat seborrhoea, acne and androgenic hair loss successfully within 7 months treatment[6].

The antifungal drug ketaconazole was found to inhibit biosynthesis of adrenal and gonadal testosterone but its potential hepato toxicity made physicians reluctant to use it as a blocker for testosterone. Other androgen receptor blockers were used to treat hirsutism such as cimetidine, cyproterone acetate and cyproheptadine[39].

3. <u>Cyproterone acetate</u> is a potent progesten and is an androgen receptor blocker. Its absorption is poor after oral dose (5 – 30% absorption) and its half life is 38 hours. Both acne and hirsutism are successfully treated with Cyproterone acetate [40,41]. The most common preparation is (2mg Cyproterone acetate plus ethinyl oestradiol 35 micro gram as an oral contraceptive) which is well tolerated and safe. Oral contraceptives reduce ovarian and adrenal hormones secretions resulting in net reduction of androgen secretion with increase in sex hormone binding globulin and minimal anti androgen side effects. It can reduce acne or hirsutism or both[42].

4. <u>Oral contraceptives</u> can be used alone or in combination with specific anti androgen. Newer formulation containing norgestimate, levonogestrel, or desogestrel stress the safety of these pills regarding lipid metabolism, risk of cardiovascular disease or breast cancer[43,44,45,46,47].

5. <u>Corticosteroides</u> are used as anti androgen to treat hirsutism. Low doses steroid given in the evening suppresses morning ACTH release and result in suppression of adrenal androgen production.

6. <u>5 Alpha reductase inhibitor (Finasteride):</u>

Two enzymes of 5 á reductase exist:

Type "one": is the dominant form in the scalp and other non genital skin.

Type "two": is the dominant form in the genital skin and Prostate [49,50].

Finasteride blocks primarily type two iso enzyme and is used in the dose of 5 mg daily in benign prostatic hyperplasia with minimal side effects.

Male pattern alopecia is treated with 1 mg daily, it is contra indicated in women in child bearing because of its potential effect on the fetus.

7. <u>Gonadotrophin releasing hormone agonists</u> are decapeptides resembling native gonadotrophin releasing hormone and are used to reduce lutenizing hormone and follicle stimulating hormone released by the pituitary gland. They are used to treat non dermatologic conditions such as precocious puberty, prostatic carcinoma, benign prostatic hyperplasia, endometriosis, uterine fibroids and polycystic ovaries syndrome.

One can conclude that low dose Spironolactone is a safe, well tolerated and effective treatment of acne in adult women and may be used as a single drug therapy or as adjunctive treatment.

Because of the favorable results reported, we planned to try Spironolactone in treatment of late onset acne in adult women using 100 mg daily dose in a prospective open trial without any other adjunctive systemic treatment and all patients chosen for the trial used topical treatment as well.

<u>Patients and Method</u>:

Patients to be treated with Spironolactone alone were chosen according to the following items or criteria:

1. Female who had acne that began to appear after the age of 20.
2. All patients had inflammatory papulopustular or nodular acne of moderate or great severity affecting lower face, mandibular region and the chin.
3. Patients giving history of premenestrual aggravation or menestrual irregularity.
4. Failure of response to acne treatment including systemic antibiotic and isotretinoin.
5. Increased oiliness and/or hirsutism of the face and/or androgenic alopecia.

Each patient has a sheet of personal data which includes (Name – Age – Sex – Occupation – Date)

- Age of onset of acne
- Duration of acne
- Degree of acne
- Is there premenstrual aggravation
- Is there associated menstrual irregularity
- Any association with:
  1. Hirsutism
     yes no
  2. Oiliness of the skin
     yes no
  3. Frontal alopecia
     yes no
- Previous treatments
  - Antibiotic
  - Roaccutane
  - Topical
  - Others
- Duration of previous treatment
- Result of treatment
- Vital signs: Pulse Blood Pressure
- Investigation : C.B.C.
  Biochemistry
  Hormonal: D.H.E.A.S
  Prolactin
  Testosterone
  Progesterone
  Estrogen

  Ultra Sound if needed for ovary and lower abdomen

<u>Performed Study</u>:

Total number of patients were 19 Females from 20 to 47 years old.

Total Average Age 31 years

Average Age of Onset	- 9 patients the acne started in early twenties - 1 patient in mid twenties - 9 patient late onset acne average 35 years old
Duration of Acne	- 12 patients 4.5 years - 5 patients 13 years - 2 patients 22 years
Degree of Severity	- 6 patients had sever acne - 13 patients had moderate acne

Premenestrual Aggrivation

- 5 patients positive
- 14 patients negative

Association with hirsutism

- 7 patients positive
- 12 patients negative

Association with Frontal Alopecia

- 2 patients positive

Association to Polycystic ovary disease

3 of our patients had Polycystic ovary diagnosed by Ultra Sound.

Previous Treatment and Response:

- 10 of the patients received oral antibiotic mainly Minocycline 100 mg 3 to 4 months with topical treatment as Dalacin solu
- 7 patients received only topical treatment like Fucidin cream, Clindacin-T solution (Clindamycin phosphate), and Benoxyl 5 cream. Those patients had no improvement.
- 2 patients received Roaccutane 0.5 mg/ kg of body weight per day for several months. Those patients had marked improvement and recurrence of acne after one year.

Spironolactone given as 100 mg daily and checked monthly:

Vital Signs: Blood Pressure taken before and after treatment of Spironolactone, no change was reported in their blood pressure.

Study Results:

1. 6 patients from 19 cured. All lesions were cleared 100 %. Improvement of acne, oiliness of face, frontal alopecia and hirsutism after 4 to 6 months of Spironolactone.
2. 8 patients had marked improvement more than 50 % of acne and hirsutism after 3 to 4 months of treatment.
3. 3 patients had partial improvement.
4. 2 patients did not comply to the medication:

one patient discontinued treatment because she became pregnant after 2 weeks of medication. Other patient developed palpitation and dizziness.

Hormonal Assay: Before and after Spironolactone Treatment

1. Prolactin: 2 of our patients had increased Prolactin level before treatment. They showed decreased level after 3 months of treatment from 688 to 500 and from 809 to 600 respectively.
2. Estrogen: Normal before and after study.
3. Progesteron: Normal before and after study.
4. D.H.E.A.S: Normal before and after study.
5. Testosterone: 5 of our patients had high testosterone level before treatment and they showed marked improvement after treatment.

Testosterone level before and after 5 months Spironolactone:

Before	After
3.11 nmol/L	2.7 nmol/L
2.83 nmol/L	1.2 nmol/L
5.15 nmol/L	2.8 nmol/L
5.03 nmol/L	2.6 nmol/L
3.9 nmol/L	1.5 nmol/L

Discussion:

Spironolactone was used to treat hyperaldosteronism and sometimes a potassium sparing diuretic.

It reduces vascular fibroses and inhibits angiogenesis and reduces vascular tone and portal hypertension. It also reduces cardiac and vascular collagen tern over and dilates blood vessels [51].

There have been some clinical trials of Spironolactone as an anti androgen in treatment of acne and hirsutism [51]. Various substances of steroidal or non-steroidal structures may serve as an alternative for anti androgenic treatment of acne. Cemitidine or ketoconazole which has weak anti androgenic effect are not used for acne. There is evidence that isotretinoin has an antiandrogenic effect [52], but its main action is known to be inhibition of sebaceous gland [52].

Topical Spironolactone experimentally reduced sebaceous secretion [53] in animals and in young adults [54]. It acts by inhibiting dihydrotestosterone receptors in human sebaceous gland [55].

Topically applied Spironolactone has no systemic side

effects but was reported that it may cause contact dermatitis [56].

Since 1978, many studies have been concluded to determine the effectiveness of Spironolactone on hirsutism and acne [57].

In vitro stimulation of sebocyte proliferation by androgen could be completely abolished by Spironolactone [58]. Anti androgens were used to treat adult females[4].

38 premenopausal females with acne were treated with Spironolactone 50 mg twice daily. 33 patients continued to follow up and 32 of them showed improvement of their acne and the adverse effects reported in this group were headache, abdominal cramp, facial swelling and metrorrhagea [59], agranulocytosis, urticaria, drug fever, irregular menses and post menopausal bleeding [60] and mild gynaecomastia in males[61].

Spironolactone may be combined with dexamethasone as a safe agent to suppress elevated dehydroepiandrosterone sulfate (D.H.E.A.S) in patients with androgenic disorders and women with elevated D.H.E.A.S without significant side effect. The average daily dose of Dexamethazone is 0.25 mg daily [62].

Spironolactone was used to treat rosacea given 50 mg daily for 4 weeks and was effective in 13 male patients [63].

Bromocriptine was used to treat late onset acne and idiopathic hyperprolactenemia [64].

Conclusion:

The use of Spironolactone in tratment of late onset acne in adult females is a safe effective treatment in the dose of 100 mg per day and was found to be effective in acne within the first months while hirsutism needs 6 months [65].

References:

1. *Clearihan L: Acne Myths and management issues. Curt Gam. Physician 2001; 30:1039-44*
2. *Goulden V; Clarl SM; Cunliffe WJ: Post-adolescent acne: a review of clinical features. Br. J. Dermatol 1997; 136:66-70.*
3. *Shaw J.C.: Low dose adjunctive spironolactone in the treatment of acne in women: A retrospective analysis of 85 consequently treated patients. J. Am. Acad. Dermatol, 2002; 43:498-502.*
4. *Thiboutor D: Hormones and acne: pathophysiology, clinical evaluation and therapies. Semin. Cutan. Med. Surg., 2001; 20:144-53.*
5. *Redmond GP; Bergfeld WF: Treatment of androgenic disorders in women: acne, hirsutism and Alopecia. Cleve-Clin-J-Med., 1990; 57 (s): 428-32.*
6. *Cusan L; Dupont A; Belangee A; et al: Treatment of hirsutism with pure antiandrogen flutamide. J. Am. Acad. Dermatol, 1990; 23 (3pt1): 462-9.*
7. *Shaw J.C.: Antiandrogen and hormonal treatment of acne. Dermatol Clin, 1996; 14:803-11.*
8. *Brest AN: Spironolactone in the treatment of hypertension: a review. Clin. Ther. 1986; 8:6-85.*
9. *Lant A: Diuretics: clinical pharmacology and therapeutic use (part III) Drugs, 1985; 29: 162-88.*
10. *Shaw J.C.: Spironolactone in dermatologic therapy. J. Am. Acad. Dermatol, 1991; 24:236-43.*
11. *Shaw J.C.: Antiandrogen in dermatology. Int. J. Dermatol 1996; 11: 770-8.*
12. *Corvol P; Michaud A; Menard J; et al: Antiandrogenic effect of spironolactones: Mechanism of action. Endocrinology 1975; 97:52-8.*
13. *Menard RH; Stripp B; Gillette JR: Spironolactone and testicular cytochrome p-450: decreased testosterone formation on several species and changes in hepatic drug metabolism. Endocrinology 1974; 94: 1628-36.*
14. *Menard RH; Loriaux DL; Bartter Fc; et al: The effect of the administration of spironolactone on the concentration of plasma testosterone, estradial and cortisol in male dogs. Steroid 1978; 31:771-82.*
15. *Loriaux DL; Menard R; Taylor A; et al: Spironolactone and endocrine dysfunction. Ann Intern. Med, 1976; 85:630-6.*
16. *Stripp B; Taylor AA; Barttec JR; et al: Effect of spironolactone in man. J. Clin. Endocrinol Metab, 1975; 41:771-81.*
17. *Tidd MJ; Horth CE; Ramsay LE; et al: Endocrine effects of spironolactone in man. Clin. Endocrinol (OXF), 1978; 9: 389-99.*
18. *Weiner IM; Mudge GH: Diuretics and other agents employed in the mobilization of edema fluid. In:Gilman AG; Goodman LS; Ra; TW; et al eds. The pharmacologic basis of therapeutics 7th Ed. New York: Macmillan, 1985; 900-1.*
19. *Sudee W; Reiyelman S; Jones SC: Disposition of tritium labeled spironolactone in dog J. Pharm. Sci, 1972; 61:1132-5.*
20. *Sadee W; Reigelman S; Jones SC: Plasma level of spironolactone in dog. J. Pharm. Sci, 1972; 61: 1129-31.*
21. *Apermann JA; Coak C; Pipere; et al: Comparative metabolism of Spironolactone and potassium canrenoate: current date in experimental animals and man. J. Drug Dev., 1987 1 (Suppl 2); 14-19.*
22. *Gardiner P; Schrode K; Qui lan D; et al: Spironolactone metabolism: steady state serum levels of the sulfur-containing metabolites. J. Clin. Pharmacol, 1989; 29:342-47.*

23. Cumming DC; Rebar RW; Hopper BR; et al: Evidence of an influence of the ovary on circulating dehydroepiandrosterone sulfate level.
J. Clin. Endocrinol Metab, 1982; 59:1069.

24. Califano L; Cannavo S; Siragusa M; et al: Esperenze nella terapia dell, acne con in trattimento topico antiandrogeno base to spironolactone (experience in the therapy of acne with topical administration of spironolactone as an antiandrogen).
Ter. 1990; 135(3): 193-9.

25. Lucky AW: Topical antiandrogens. Arch. Dermatol 1985; 121: 55-6.

26. Messina M; Manieri C; Rizzi G; et al: A new therapeutic approach to acne: an antiandrogen percutaneous treatment with spironolactone curr.
Ther. Res. 1983; 34:319-24.

27. Hughes BR; Cunliffe WJ: Tolerance of spironolactone.
Br. J. Dermatol, 1988; 118: 687-91.

28. Greenblatt DJ; Koch-Weser J: Adverse reactions to spironoladone.
JAMA 1973; 225:40-3.

29. Burke BM; Cunliffe WJ: Oral spironolactone therapy for female patients with acne, hirsutism or androgenic Alopecia [letter].
Br. J. Dermatol 1985; 1t2: 124-25.

30. Wagner BM: Long term studies of spironolactone in animals and comparison with potassium canrenoate.
J. Drug. Dev, 1987; 1(Suppl 2): 7-11.

31. Barker DJP: The epidemiologic evidence relating to spironolactone and malignant disease in man.
J. Drug. Dev. 1987; 1 (Suppl 2): 22-25.

32. Goodfellow A; Alaghband Zadeh J; Carter G; et al: Oral spironolactone improves acne Vulgaris and reduces sebum excretion.
Br. J. Dermatol, 1984; 111:124-5.

33. Muhlemann MF; Carter GD; Cream JJ; et al: Oral spironolactone: an effective treatment for acne Vulgaris in women.
Br. J. Dermatol, 1986; 115: 227-32.

34. Cusan L; Dupont A; Gomez JL; et al: Comparison of flutamide of hirsutism. A randomized controlled trial.
Fertil steril 1994; 61:281-87.

35. Motta T; Maggi G; Azzolari E; et al: Flutamide in the treatment of hirsuitism.
Int. J. Gynaecol Obstet, 1991; 32:155-57.

36. Gomez JL; Dupont A; Cusan L; et al: Incidence of liver toxicity associated with the use of Flutamide in prostate cancer patients.
Am. J Med, 1992; 92:465-70.

37. Wysowski DK; Freiman JP; Tourtelot JB; et al: Fatal and nonfatal hepatoxicity associated with flutamide.
Ann. Intern. Med, 1993; 118:860-64.

38. Schurmeyer T; Nieschlag E: Effect of Ketoconazole and other imiduzole fungicides on testosterone biosynthesis.
Acta Endocrinol (Copenh), 1984; 105:275-80.

39. Loy R; Seibel MM: Evaluation and therapy of polycystic ovarian syndrome. Endocrinal-Metab-Clin-North-Am, 1988; 17(4): 785-813.

40. Brein RC; Cooper ME; Murray RML; et al: Comparison of sequential cyproterone acetate/estrogen versus spironolactone/oral contraceptive in treatment of hirsutism.
J. Clin. Endocrinol Metab, 1991; 72:1008-13.

41. Muller JA; Wojnarowska FT; Dowd PM; et al: Antiandrogen treatment in women with acne: A controlled trial.
Br. J. Dermatol, 1986; 114:705-16.

42. Lemay A; Dewailly SD; Grenier R; et al: Attenuation of mild hyperandrogenic activity in post pubertal acne by triphasic oral contraceptive containing low doses of ethynyl estradiol and d.I-nogesteral.
J. Clin. Endocrinol Metab, 1990; 71:8-14.

43. Janaud A; Rouffy J; Upmalis D; et al: A comparison study of lipid and androgen metabolism with triphasic oral contraceptive formulations containing norgestimate or levonogestul. Acta Obstet Gynecol Scand, 1992; 71 (suppl): 33-38.

44. Darney P: Safety and efficacy of a triphasic oral contraceptive containing desogestrel. Results of three multicenter trials contraceptive 1993; 48:323-37.

45. Hawley W; Nuovo J; De Neef CP; et al: Do oral contraceptive agents affect the risk of breast cancer? A meta analysis of the case control reports.
J. A. Board Fam. Prac, 1993; 6:123-35.

46. Lemay A; Poulin Y: Oral contraceptives as antiandrogenic treatment of acne.
J. Obstet Gynaecol Can, 2002; 24(7): 559-67.

47. Freeman EW; Kroll R; Rapkin A; et al: Evaluation of a unique contraceptive in the treatment of premenstrual dysphoric disorder.
J. Womans-Health-Gend-Base of Med, 2001; 10: 561-9.

48. Rittmaster RS; Givner ML: Effect of daily and alternate day low dose Prednisone on serum cortisol and adrenal androgens in hirsute women.
J. Clin. Endocrinol Metab, 1988; 67:400-03.

49. Rittmaster RS: Finasteride.
N. Engl. J. Med, 1994; 330:120-125.

50. Thigpen AE; Silver RI; Guileyardo JM; et al: Tissue distribution and ontogeny of steroid 5-a redactor is enzyme expression.
J. Clin. Invest, 1993; 92:903-10.

51. Doggrell SA; Brown L: The spironolactone renaissance.
Expert-Opin-Investig. Drugs, 2001; 10(5): 943-54.

52. Schmielt JB: Other antiandrogens Dermatology 1998; 196: 17-153.

53. Seki T; Toyomota T; Morohashi M: effects of topically applied spironolactone on androgen stimulated sebaceous glands in the hamster pinna.
J. Dermatol, 1995; 22(4): 233-7.

54. Yamamota A; I to M: Topical spironolactone reduces sebum secretion rates in young Adults.
J. Dermatol, 1996; 23(4): 243-6.

55. Berardesca E; Gabba P; Ucci G; et al: Topical spironolactone inhibits dihydrotestosterone receptors in

human sebaceous glands: an autoradiographic study in subjects with acne Vulgaris.

Int J. Tissue React. 1988; 10(2): 115-9.

56. *Corazza M; Strumia R; Lombardi AR; et al: Allergic contact dermatitis from spironolactone contact Dermatitis, 1996; 35(6): 365-6.*
57. *Lee O; Farquhar C; Toomath R; et al: Spironolactone versus placebo or in combination with steroids for hirsutism and or acne.*

Cochranes – Database-Sys-Rev., 2002; (2): CD000194.

58. *Zouboulis CC; X1a-L; Akamatse H; et al: The human sebocyte culture model provides new insights into development and managements of seborrhea and acne.*

Dermatology 1998; 196: 21-31.

59. *Lubbos HG; Hasinski S; Rose L; et al: Adverse effects of spironolactone therapy in women with acne.*

Arch. Dermatol, 1998; 134:1162-63.

60. *Jurzyk RS; Spielvogel RL; Rose LI: Antiandrogens in the treatment of acne and hirsutism.*

American Family Physicina, 1992; 45: 1803-6.

61. *Laue L; Kenigsberg D; Pescovitz OH; et al: Treatment of familial male precocious puberty with spironolactone and testolactone.*

The New England J. of Medicine, 1989; 320:496-502.

62. *Redmond GP; Gidwani GP; Gupta MK; et al: Treatment of androgenic disorders with dexamethasone –Dose Response relationship for suppression of dehydroepandrosterone sulfate.*

J. Am. Acad. Dermatol, 1990; 22: 91-3.

63. *Hizawa H; Niimura M: Oral spironolactone therapy in male patients with rosacea.*

J. Dermatol, 1992; 19(2): 293-7.

64. *Peserico A; Ruzza G; Fornasa CV; et al: Branocripline treatment in patients with late onset acne and idiopathic hyperprolactenemia.*

Acta Der Venereal. (Stockh), 1983; 68:83-84.

65. *Pugeat M; Emidani M; Deckhand H; et al: Treatment of hirsutism with spironolactone and progestagen combination.*

Presse-Med, 1990; 19(33): 1529-32.