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New Developments in Hormonal Therapy for Acne

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ABSTRACT

Oral contraceptives (OCs) are a valuable option for the treatment of women with acne. The use of OCs can be considered across the spectrum of acne disease severity in women. In Canada, three preparations are approved for mild-to-moderate acne, and a fourth is indicated for severe acne. These formulations contain estrogen in the form of ethinyl estradiol and a progestin. In Canada, the most recently approved OC is ethinyl estradiol 0.03mg and drospirenone 3mg (Yasmin®, Bayer). With the accumulating evidence on the efficacy and safety of drospirenone-containing hormonal preparations, this formulation provides dermatologists with a new treatment option for acne and other hyperandrogenic disorders.

Key Words: *Acne vulgaris, oral contraceptives, ethinyl estradiol, cyproterone acetate, drospirenone, norgestimate, levonorgestrel*

For many years, oral contraceptives (OCs) have been used by dermatologists as a treatment option for women with acne. OCs that are indicated for use in acne are effective across the spectrum of disease severity:

- in mild acne as an adjunct to topical therapy for female patients desiring contraception
- in moderate acne as a form of systemic therapy
- in severe acne
  - as a primary form of therapy
  - as one of two preferred forms of contraception in women treated with systemic isotretinoin.

From their inception, these preparations have evolved to include less estrogen and incorporate progestins with less intrinsic androgenicity. These modifications were undertaken to reduce the potential risk of thromboembolic events, hepatic tumors, hypertension, altered glucose metabolism, and androgenic side-effects.

OCs for the Treatment of Acne

In Canada, four hormonal preparations are presently indicated for the treatment of acne. These preparations all contain estrogen and progestins with either minimal androgenicity (i.e., ethinyl estradiol/ norgestimate, and ethinyl estradiol/ levonorgestrel) or antiandrogenic potential (i.e., ethinyl estradiol/ cyproterone acetate, and most recently, ethinyl estradiol/ drospirenone). Their demonstrated efficacy and long-term safety profile advocate their use in various grades of acne in women. Evidence supporting the use of these agents in acne was recently reviewed in the *Journal of Cutaneous Medicine and Surgery*,[1] and is summarized briefly here.

Ethinyl Estradiol/ Norgestimate (Ortho Tri-Cyclen®)

Ethinyl estradiol 0.035mg with norgestimate in increasing doses, 0.180mg/ 0.215mg/ 0.250mg (Ortho Tri-Cyclen®, Ortho-McNeil), was shown to be efficacious in moderate facial acne in two randomized placebo-controlled trials involving 324 subjects who were treated for 6 cycles.[2,3] Significant improvements in lesion counts and investigator global assessment scores were observed. Inflammatory lesions were reduced by 56%, noninflammatory lesions by 41%, and 32% achieved excellent improvement. Norgestimate has low intrinsic androgenicity with low binding affinity for androgen receptors, whereas it is strongly selective and avidly bound to progesterone receptor sites.

Ethinyl Estradiol/ Levonorgestrel (Alesse®)

Ethinyl estradiol 0.020mg and levonorgestrel 100µg (Alesse®, Wyeth Canada) was shown to be efficacious in moderate facial acne in two randomized placebo-controlled trials involving 721 women who were treated for 6 cycles.[4,5] Significant improvements were noted in lesion count, with reduction in acne counts of: 32%–47% inflammatory, 13%–25% noninflammatory, and 23%–40% total lesions. Investigator global assessment scores were rated as clear to almost clear in 48%-58% of subjects.

Ethinyl Estradiol/ Cyproterone Acetate (Diane-35®)

The combination of ethinyl estradiol 0.035mg and cyproterone acetate 2mg (Diane-35®, Bayer Healthcare) has been available as a hormonal treatment for acne in Canada since 1998. Cyproterone acetate is an analogue of hydroxyprogesterone and has progestational activity. It acts as a potent antiandrogen by competitive inhibition of testosterone and DHT binding to the androgen receptor and by inhibiting gonadotropin secretion. The best current evidence for the efficacy of this OC is in the treatment of mild-to-moderate facial acne, and is derived from trials with relatively small sample sizes, variable efficacy outcomes, varying trial durations, and the absence of placebo-controls.[1]

Drospirenone

Spironolactone, a synthetic steroid, is an antiandrogen that competitively binds to androgen receptors, inhibits 5α-reductase activity, and reduces androgen biosynthesis. This agent, in doses of 50-200mg/day, has been shown to be efficacious for acne, although the trials have been small, and differed in dosages evaluated, outcome parameters, and reporting methodology.[1] Drospirenone (DRSP) is a novel progestogen derived from spironolactone and has both antiandrogenic and antimineralocorticoid activity. DRSP 3mg has been combined with two different doses of ethinyl estradiol: 0.030mg for Yasmin®, Bayer HealthCare; and 0.020mg for YAZ®, Bayer Schering Pharma AG. Yasmin® was recently approved for the treatment of acne in Canada, while both formulations are available in the US. For antimineralocorticoid activity, the dose equivalence for DRSP 3mg is spironolactone 25mg.[6]

Ethinyl Estradiol/ Drospirenone (Yasmin®)

The efficacy of Yasmin® for treating acne vulgaris was evaluated in a randomized controlled trial with Diane-35® as the active comparator. One hundred and twenty-five subjects aged 16-35 years with mild-to-moderate facial acne were recruited for a 9-cycle duration trial. Median reduction in total facial acne lesions was 62% for Yasmin® and 59% for Diane-35® after 9 cycles. Thus, Yasmin® was found to be as efficacious as Diane-35® in the treatment of acne. Both preparations were well-tolerated, with adverse events being mild-to-moderate in intensity and typical of those associated with OCs.[7]

The safety of OCs containing ethinyl estradiol 0.030mg and DRSP 3mg was compared with other OCs in a European multinational, prospective, observational, new-user cohort study.[8] A total of 58,674 women were observed for 142,475 women-years. Serious adverse and fatal events were rare. Regression analysis of adverse cardiovascular events yielded hazard ratios for DRSP-containing OCs vs. levonorgestrel-containing and other OCs of 1.0 and 0.8 (upper 95% confidence limits, 1.8 and 1.3) for venous, and 0.3 and 0.3 (upper 95% confidence limits, 1.2 and 1.5) for arterial thromboembolism, respectively. Thus, the risks of adverse cardiovascular and other serious events in users of DRSP-containing OCs were found to be similar to those associated with other OCs.

Yasmin® has also been studied in other conditions associated with hyperandrogenism. Woman with polycystic ovary syndrome (PCOS) have elevated androgen levels that can cause acne, hirsutism, alopecia, weight gain, irregular menstruation and infertility. In an open-label study of PCOS, 20 women with this condition were evaluated over six cycles.[9] At the end of the study, significant improvement was observed in lowered serum testosterone levels and increased sex hormone-binding globulin levels. In another study of women with PCOS, levels of androstenedione, dehydroepiandrosterone sulfate, testosterone, and free testosterone were reduced when treated with Yasmin®.[10]

Ethinyl Estradiol/ Drospirenone (YAZ®)

YAZ® combines ethinyl estradiol 0.020mg and drospirenone 3mg in a 24/4 active/inert oral contraceptive regimen. In the US, this OC is indicated for premenstrual dysphoric disorder. In January 2007, US FDA approval was obtained for moderate acne that

was based on the results of two multicenter, double-blind, randomized, placebo-controlled studies.[11] These trials involved a total of 889 subjects with moderate acne, ranging from 14-45 years of age, who were randomized to receive YAZ® or placebo for six 28-day cycles. A rating of clear/ almost clear on the Investigator Global Assessment was observed in 18% of YAZ®-treated subjects compared with 6% on placebo. Mean reduction in inflammatory lesion counts was 15 (49%) in YAZ®-treated subjects compared with 11 (33%) on placebo. Total lesion and non-inflammatory count changes were similar in both groups.

Conclusion

The accumulating evidence on the efficacy and safety of DRSP-containing hormonal preparations for these indications provides dermatologists with a new option for the treatment of acne and other hyperandrogenic disorders.

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TNF-α Inhibitors in Dermatology

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ABSTRACT

To date, the US FDA has approved three tumor necrosis factor (TNF)-α inhibitors for use in dermatology. Etanercept (Enbrel®, Amgen-Wyeth), a fully human fusion protein of TNF receptor II bound to the Fc component of human IgG1, is approved for use in psoriasis (2004) and psoriatic arthritis (2002). Infliximab (Remicade®, Centocor) is a chimeric monoclonal antibody that is approved for use in psoriasis (2006) and psoriatic arthritis (2005), and adalimumab (Humira®, Abbott Laboratories), a fully human monoclonal antibody, is approved for use in psoriatic arthritis (2005). While data regarding the efficacy and safety of these therapies is abundant, it proves nearly impossible to objectively compare and contrast agents as there are no head-to-head trials. Clinical experience and post-marketing reporting has allowed dermatologists to identify the relative strengths and limitations of each agent. The well-founded enthusiasm for these agents, because of their excellent initial efficacy and safety profile, is reasonably tempered by concerns about declining efficacy over time, the risk of infection, lymphoma and demyelinating disorders, and cost. The distinct and targeted mechanism of action of the TNF inhibitors allows dermatologists to customize therapy to match the individual needs and characteristics of patients who are candidates for systemic or phototherapy.

Key Words: *TNF inhibitors, tumor necrosis factor, etanercept, infliximab, adalimumab*

Efficacy

The efficacy of the tumor necrosis factor (TNF) inhibitors for the treatment of chronic plaque psoriasis and psoriatic arthritis has been well established in clinical trials and through real world experience. The improvements in the psoriasis area and severity index (PASI) and American College of Rheumatology (ACR) scores are comparable, and in many cases superior, to traditional antipsoriatic drugs and disease-modifying antirheumatic drugs (DMARDs), respectively. Clinical trials also demonstrate improvement in physical and health-related quality of life (HRQoL) measures in psoriasis patients who were treated with biologics when compared with placebo.[1]

Long-term studies objectively demonstrating continued efficacy for plaque-type psoriasis are limited, given the relatively recent FDA approval of the individual agents for this use. Tyring and colleagues recently reported extended efficacy of etanercept (50mg twice weekly) out to 96 weeks of continuous therapy.[2] Clinical experience suggests that a percentage of patients on long-term therapy with TNF inhibitors may begin to show a decline in original efficacy. Long-term trial data is necessary to further explore this clinical observation.

Safety

Assessing efficacy of the TNF inhibitors from trial data is accomplished with relative ease, while safety assessments are much more difficult. Interdrug comparison is difficult because of the lack of head-to-head trials, the differences in trial design and patient characteristics, and the lack of consistency in mandatory postmarketing reporting of adverse events. Anti-TNF agents act with greater target specificity than traditional systemic agents and to date, more than 1 million patients have been exposed across indications, allowing a reasonable degree of confidence in the safety of these drugs. Given the molecular role that TNF plays in the immune system, the primary safety concerns regarding the use of these drugs include risk of infection and malignancy.

Adverse Events

The most common adverse events in the short-term are injection site (etanercept and adalimumab) and infusion reactions (infliximab). The most concerning short-term risk is serious infection, which includes sepsis, infection from opportunistic organisms, and reactivation of latent tuberculosis. All anti-TNF agents carry a warning about reactivation of tuberculosis (black box for infliximab and adalimumab; bold letter for etanercept).[3-6] The risk of infection is higher in patients with predisposing underlying conditions, such as diabetes mellitus, congestive heart failure, a history of active or chronic infections, or concurrent use of immunosuppressive drugs.

Other Safety Concerns

Other class-wide safety concerns include the risk of malignancy, demyelinating disease, and exacerbation or development of congestive heart failure.[7,8] The risk of lymphoma among patients treated with anti-TNF agents remains controversial. The incidence of lymphoma was higher in anti-TNF treated patients compared with controls during the controlled portion of trials of all

approved agents. In patients with psoriasis, no clear findings identify whether lymphoma risk is associated with disease severity, treatment, other unidentified factors, or a combination of factors.[9] To date, there is no consensus on the estimated risk of lymphoma with anti-TNF therapy. Although nonmelanoma skin cancer and lymphoma rates are greater in patients treated with anti-TNF agents, conclusions are difficult to draw in light of the pre-existing association of lymphomas with severe rheumatoid arthritis, psoriasis, and systemic inflammation. Furthermore, prior systemic therapies and environmental risk factors, such as sun exposure and smoking, confound the data. National registries to date show no increase in solid cancers vs. the general population.

Demyelinating Diseases

TNF has been implicated in multiple sclerosis (MS) pathogenesis, has been identified in active MS lesions, and is known to be toxic to oligodendrocytes *in vitro*. A double-blind, placebo-controlled phase II study of an anti-TNF molecule (lenercept, a recombinant TNF receptor p55 immunoglobulin fusion protein) conducted in MS patients documented significantly increased and earlier occurrences of MS exacerbations and more severe neurologic deficits in the lenercept treatment groups compared to placebo.[10] Although a causal relationship between TNF inhibitors and demyelinating disease remains unclear, optic neuritis, transverse myelitis, MS, seizures, and Parkinson's disease have been reported in patients taking TNF inhibitors. The drugs should be withheld from any patient who has a history of, or first degree relative with a demyelinating disease; Patients should be monitored vigilantly for suspicious signs or symptoms.

Congestive Heart Failure

TNF inhibitors were previously evaluated as a therapy for congestive heart failure (CHF), but trials were halted due to lack of efficacy. Although data from one of the etanercept CHF trials suggested higher mortality in treated patients vs. placebo, analyses did not identify any specific risk factors. Postmarketing reports of CHF have included:

- new onset cases
- cases with no identifiable risk factors, such as previous myocardial infarction, coronary artery disease, or hypertension
- cases in patients under the age of 50.[11]

Most patients improved or symptoms resolved once therapy was stopped, though rare fatal incidences have been recorded.

Autoimmunity

The issue of autoimmunity requires further study. Autoantibody formation (ANA, anti-dsDNA, and anticardiolipin) appears to be more common with infliximab than with etanercept; only limited reports exist for adalimumab. Development of human antihuman antibodies and human antichimera antibodies also seem to be slightly more common with infliximab than with other agents. Infliximab data suggests that development of these antibodies is loosely associated with reduced efficacy and a higher incidence of infusion reactions.[12] The impact of long-term treatment with anti-TNF agents on the development of autoimmune diseases is unknown.

Pregnancy and Breastfeeding

All anti-TNF agents are pregnancy category B (no human studies conducted, but no adverse effects noted in animal studies). Because human data is not available, therapy should be avoided, if possible, in pregnant or breastfeeding women.

Primary Issues of Concern

Two primary issues of concern facing the clinicians who are prescribing these agents include long-term safety and the appropriate choice of screening/monitoring tests. Long-term safety profiles remain to be established. Patient selection is key; not all patients are good candidates for treatment with anti-TNF agents. Patients must be predetermined to be reliable, compliant with follow-up visits, and able to self assess and report the onset of new signs or symptoms that may herald the onset of an adverse event. Although guidelines regarding objective screening and monitoring are yet to be established, a reasonable approach includes a detailed history and physical examination, TB testing (US FDA-mandated for adalimumab and infliximab), and additional baseline lab tests that are deemed appropriate as a result of the history and examination. Close and routine follow-up is warranted to assess both the continued efficacy and safety of these drugs in individual patients.

Cost

Compared with traditional treatments for psoriasis, such as phototherapy and methotrexate, treatment with the anti-TNF drugs represents a tremendous financial burden. A year of methotrexate at 15mg/week costs an average of $375 USD (not including lab fees), while a year of biologic therapy can vary between $10,000 USD and $25,000 USD (or more) based on the dosage and treatment regimen prescribed.[13] Moreover, insurance carriers often require failure of, or contraindications to, one or more standard

therapies prior to approval of coverage for a biologic agent, thus presenting a major obstacle to patients in need. Cost is not only a concern to patients, but to their dermatologists and the entire healthcare system in general. The cost of treatment is a primary reason many dermatologists do not consider biologic agents as first-line therapy for moderate-to-severe or socially disabling psoriasis, and reinforces the first-line use of more traditional, efficacious, and cost effective treatments such as ultraviolet light.[14] In the case of psoriatic arthritis, however, the low cost of time-proven agents, such as methotrexate, may no longer be considered worth the risk of potential toxicity.

Conclusion

The discovery, use, and great clinical success of anti-TNF molecules for the treatment of moderate-to-severe psoriasis and psoriatic arthritis have engendered well-founded enthusiasm, but the cost of therapy and unknown long-term safety and efficacy profile gives us pause. The addition of these agents to the available therapeutic modalities for treating psoriasis, which can be physically, psychologically, and socially devastating, is excitedly welcomed. However, as with any new drug class, the high price of therapy and the unknown long-term effects represent major obstacles to selection of these drugs as first-line agents in all patients with moderate-to-severe or debilitating psoriasis/ arthritis. The excellent initial efficacy seems to hold up fairly well over 12-36 months, but a trend toward declining efficacy thereafter is being observed in some cases. Combination therapy with methotrexate is observed to maintain the efficacy of infliximab, but the additional cost and risk of combination may not be appropriate for all patients.

The major focus of concern now and in the future remains safety. Objective screening and monitoring guidelines are needed, as current clinical practice varies from no screening to indiscriminate panel testing. Given safety data, including postmarketing reports, a reasonable approach to patient selection and monitoring includes specific tests for all patients and additional tests based on individual patient need. A thorough history and physical examination with careful assessment for neurologic abnormalities and a baseline tuberculin skin test (PPD), complete blood count, and metabolic profile are a minimum. Additional laboratory testing and subsequent monitoring should be selected individually given the patient, region of practice, and drug to be utilized. Frequent in-office follow-up to assess efficacy and safety is warranted.

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Class	Name/Company	Approval Dates and Comments
Antiacne Agent	**Adapalene** *Differin® Gel 0.3%* Galderma Laboratories	The US FDA approved a higher concentration formulation of this topical retinoid in June 2007 for the treatment of moderate-to-moderately severe acne.
Biologic	**Adalimumab** *HUMIRA®* Abbott Laboratories	The European Commission granted marketing authorization in June 2007 for the use of this self-administered biologic for the treatment of Crohn's disease.
Dermal Filler	**Hyaluronic Acid Injectable Soft Tissue Filler** *ELEVESS®* Anika Therapeutics/ Galderma	The US FDA approved this soft tissue filler in July 2007 for the treatment of facial wrinkles and scar remediation.
Antifungal Agent	**Ketoconazole** *Extina® Foam 2%* Stiefel Laboratories	The US FDA approved this product in July 2007 for the topical treatment of seborrheic dermatitis in immunocompetent patients 12 years of age and older. Extina® is administered using VersaFoam® HF® technology, a topical drug delivery vehicle that is quickly absorbed into the skin. Studies show consistent skin permeation, drug distribution, and drug delivery.

Drug News

Treatment for Lupus Nephritis	In June 2007 Aspreva Pharmaceuticals and Roche released preliminary results for a clinical trial comparing oral mycophenolate mofetil (MMF) (CellCept®) with IV cyclophosphamide (IVC), which is the current standard of care for inducing treatment response in the induction phase of patients suffering from lupus nephritis. Although response rates were similar in both arms, the trial did not meet its primary objective of demonstrating that MMF was superior to IVC in inducing treatment response in this disease. Additional analyses are ongoing to determine the potential for a regulatory submission.
Dermal Fillers	According to an addendum in *The Medical Letter**, some consultants for the publication have suggested that their recent article on dermal fillers (Dermal Fillers. *Med Lett Drugs Ther* 49(1260):39-40 [2007]) should have included stronger warnings about the risk of fillers that are not biodegradable, such as Artefill®. Even with the best technique, the polymethylmethacrylate (PMMA) beads in this product can, over time, cause foreign-body granulomas and hypertrophic scarring, which may require surgical removal. Granulomas and nodules have been especially frequent when Artefill® was injected into the lips. Complications are less likely with hyaluronic acid products such as Hylaform®, Juvederm®, or Restylane®. **Med Lett Drugs Ther* 49(1265):60[2007]

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