Systemic therapy for acne vulgaris

Alison M Layton

There are three main groups of systemic therapies available for the treatment of acne vulgaris: systemic antibiotics, hormonal therapy (for females) and oral isotretinoin. This article outlines when these treatments should be prescribed for the treatment of acne, considers the impact of therapy on aetiology, and advises on dosage regimens, potential adverse effects and expected efficacy.

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Acne vulgaris remains a common problem (*Figure 1*). Research into the pathogenesis of acne over the last few years has improved understanding and enabled clinicians to target specific aetiological factors when treating acne. Systemic therapy is generally used to treat moderate to severe inflammatory acne and should be selected to impact on the specific aetiological factors implicated in the disease process.

The central events that cause acne vulgaris are:

1. Sebaceous hyperplasia with seborrhoea
2. Abnormal follicular desquamation leading to hyperkeratinization within the sebaceous follicle
3. Colonization and proliferation of *Propionibacterium acnes* within the sebaceous duct and the generation of extracellular inflammatory products by *P. acnes*
4. Production of perifollicular inflammation.

There are three main groups of systemic therapies available for acne:

1. Systemic antibiotics
2. Hormonal therapies (for females)
3. Oral isotretinoin.

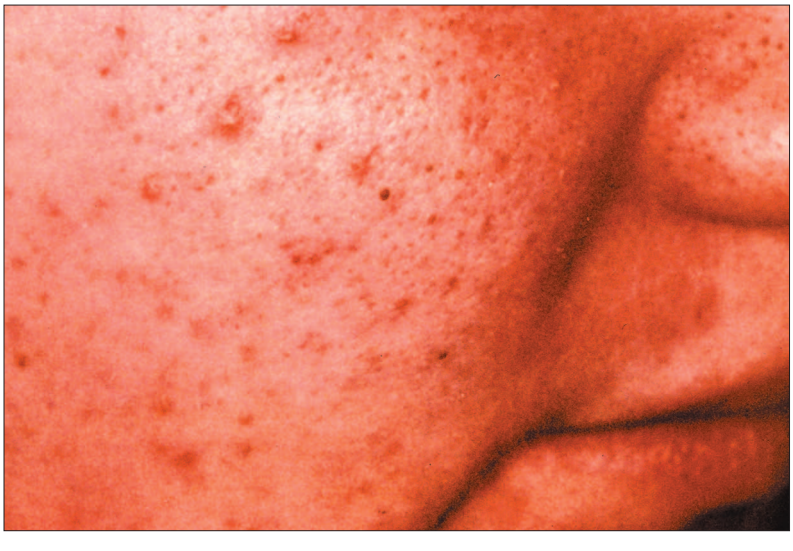

Figure 1. Acne vulgaris, mixed inflammatory and non-inflammatory lesions.

This article outlines when these respective therapies should be considered for the treatment of acne vulgaris and clarifies how the treatment modalities may be used.

SYSTEMIC ANTIBIOTICS

Systemic antibiotics remain the mainstay of oral therapy for moderate to severe inflammatory acne vulgaris (Meynadier and Alirezai, 1998; Cunliffe and Gollnick, 2001). Oral antibiotics have been shown to reduce the number of *P. acnes* (Marples and Williamson, 1969; Meynadier and Alirezai, 1998). Colonization with *P. acnes* results in secretion of extracellular enzymes, cytokines (e.g. interleukin-1α) and heat shock proteins which have mitogenic effects on T cells (Holland et al, 1993; Eady and Cove, 2000). In addition to interfering with the growth and/or metabolism of propionibacteria, antibiotics have an anti-inflammatory activity by reducing and inhibiting cytokine production, affecting macrophage functions and inhibiting neutrophil chemotaxis (Golt and Ujartanssons, 1966). Antibiotics that can both reduce the number of *P. acnes* and reduce inflammation by different mechanisms are therefore of great benefit in the treatment of moderate to severe acne.

Oral erythromycin and tetracycline have a long history of proven efficacy in the management of inflammatory acne (Golt and Ujartanssons, 1966; Meynadier and Alirezai, 1998). The use of oral macrolides (mainly erythromycin) in acne has become increasingly limited because of increasing evidence of bacterial resistance to the antibiotic. A clear correlation between erythromycin-resistant *P. acnes* and poor clinical response has being demonstrated (Eady et al, 1989). There is frequently cross-resistance between erythromycin and clindamycin. As a result of this, macrolides should be reserved for cases where cyclines are not tol-

erated or are contraindicated, for example in pregnancy, when breastfeeding and in children below the age of 8–12 years (depending on different national licences).

First generation cyclines (i.e. tetracycline hydrochloride, oxytetracycline) or second generation cyclines (doxycycline, lymecycline or minocycline) should be considered as first-line systemic antibiotic therapy when oral antibiotic therapy is required for acne. One advantage of the second generation of cyclines relates to improved absorption which is unaffected by food. This difference may improve compliance when second generation cyclines are used, particularly for adolescents. The only metabolic difference of note between individual second generation cyclines is that doxycycline is cleared by the liver, allowing this treatment to be used in patients with renal impairment.

There is a paucity of good clinical trials to confirm what is the best dosage regimen or duration for each individual treatment; however, studies examining lymecycline and minocycline suggest that patients may benefit from treatment with oral antibiotics for more than 1 month but there is little advantage in using these agents for more than 3 months (Bossuyt et al, 2003). The risk of developing antibiotic resistance is thought to occur in at least 25% of patients receiving antibiotics and is more likely to occur when treatment is prolonged (>3 months) (Eady et al, 2003). This potential problem should be taken into account when considering extending treatment beyond 3 months.

There is evidence to suggest that by selecting combined treatment regimens that impact on more than one aetiological factor improvement will be more rapid and efficacy enhanced (Cunliffe et al, 2004). This logical approach helps to minimize the duration of antibiotic exposure. An ideal approach should combine a topical retinoid with an oral antibiotic in the first instance and then use topical benzoyl peroxide to reduce the likelihood of resistance emerging in cases where antibiotics are continued (Gollnick et al, 2003). Co-trimoxazole and trimethoprim have been used as third-line agents in the treatment of acne, however, they have no product licence for this. An allergic reaction to the sulphonamide component of the co-trimoxazole may be seen in up to 3% of patients. Hence, these agents are limited to situations where other systemic antibiotics are contraindicated or there is proven to resistance to other agents.

Other systemic antibiotics shown to be effective in acne include clindamycin, but this is rarely used because of potential and serious effects including the overgrowth of *Clostridium difficile* and resultant *Pseudomonas* colitis. One Japanese study has shown quinolones to be beneficial in acne (Kawada et al, 2002). However, there is little evidence to support their use and the high cost and unsuitability of these agents for adolescents (because of their potential effects on articular cartilage) does not support the use of these drugs as a routine agent in the treatment of acne vulgaris (Drlica and Malik, 2003). *Table 1* outlines the systemic antibiotics available for treatment of acne vulgaris, outlines the optimum dosage regimen and clarifies potential adverse effects.

Antibiotic resistance

Strains of resistant *P. acnes* were first detected in the United States in the 1970s (Crawford et al, 1979). Since then resistant strains have been reported in many European dermatology departments (*Figure 2*) and across the world. A recent survey conducted throughout Europe showed that at least 50% of acne patients were colonized by erythromycin- and clindamycin-resistant strains of *P. acnes* and as many as 20% were colonized with tetracycline-resistant strains (Ross et al, 2003). This study also demonstrated that resistance was driven by antibiotic prescribing.

TABLE 1.
Systemic antibiotics for the treatment of acne vulgaris

Drug	Dosage	Comments regarding use	Incidence of *P. acnes* resistance	Adverse effects
Oxytetracycline	500 mg twice daily	Inexpensive, take 30 minutes before food and not with milk	Moderate (20%)	Rare onycholysis, photosensitivity, benign intracranial hypertension
Erythromycin	500 mg twice daily	Inexpensive	High (>50%)	Gastrointestinal upset, nausea, diarrhoea all fairly common
Minocycline	100–200 mg daily	Expensive	Low (in 1999) but increasing	Headaches (dosage-dependent), pigmentary changes, autoimmune hepatitis
Doxycycline	100–200 mg daily		Moderate	Photosensitivity (dose-dependent)
Lymecycline	300–600 mg daily	Moderate	As for oxytetracycline	Less than with minocycline
Trimethoprim	200–300 mg twice daily	Inexpensive	Low (in 1999) (12%)	Rare hepatic/renal toxicity agranulocytosis

P. acnes = Propionibacterium acnes

Longer courses are more likely to result in some degree of antibiotic-resistant *P. acnes* emerging.

It had been reported that the presence of antibiotic-resistant *P. acnes* can reduce clinical response to treatment in the case of erythromycin and tetracycline (Leyden et al, 1983; Eady et al, 1989; M Ozolins, EA Eady, A Avery, unpublished data, 2003). Hence the presence of antibiotic-resistant *P. acnes* may contribute to or cause therapeutic failure in some patients. Antibiotic-resistant strains of *P. acnes* can be transmitted between individuals and studies have shown that up to 85% of untreated close contacts of patients on long-term antibiotic treatment harbour erythromycin-resistant strains of *P. acnes* (Ross et al, 2003).

Guidelines for optimizing oral antibiotic use and preventing the emergence of resistant strains include:

1. Only use antibiotics when clinically indicated and where alternative non-antibiotic acne treatments are not expected to have the same degree of benefit
2. Only continue antibiotic therapy until you and the patient agree there is no further improvement
3. Try to avoid continuing antibiotics beyond 6 months if possible
4. If antibiotics are continued beyond 3 months, try and use antiresistant agents (topical benzoyl peroxide will reduce resistant strains at the site of its application)
5. Benzoyl peroxide applied for a minimum of 5–7 days between or during antibiotic courses will help to reduce antibiotic-resistant *P. acnes* at the site of application (Eady et al, 1994)
6. Do not switch antibiotics without adequate justification. Use the same antibiotic if patients relapse having previously responded well to the original antibiotic prescribed
7. Encourage compliance as poor compliance can predispose patients to the emergence of antibiotic-resistant *P. acnes*
8. Avoid antibiotics as monotherapy. Try and reduce antibiotic exposure by using a combined approach to therapy, i.e. prescribing topical agents along with antibiotics to enhance efficacy and expedite improvement
9. Avoid concomitant use of oral and topical therapy with chemically dissimilar antibiotics.

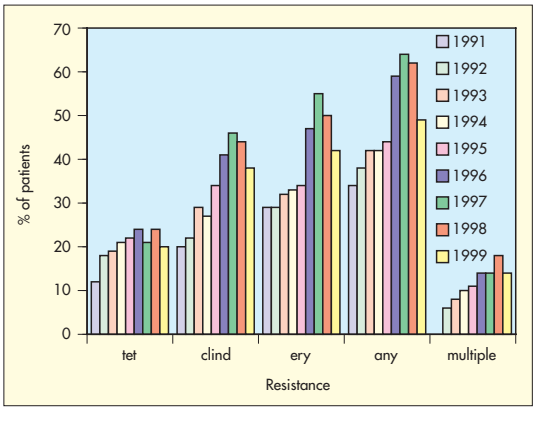

Figure 2. Prevalence of skin carriage of antibiotic-resistant* Propionibacteria *by outpatients attending the Department of Dermatology, Leeds General Infirmary. any = any antibiotic; clind = clindamycin; ery = erythromycin; multiple = multiple antibiotic regimen; tet = tetracycline.

HORMONAL THERAPY

Hormonal treatments can be very effective in females with acne, whether or not their serum androgen levels are abnormal.

Oral contraceptives

Oral contraceptives are thought to exert an anti-acne effect by decreasing the amount of circulating androgens. Specifically they increase sex-hormone binding globulin and decrease free testosterone in healthy women. In addition the oestrogen component may decrease the production of ovarian androgens by suppressing the secretion of pituitary gonadotrophins. A number of progestins also have intrinsic androgenic activity which can aggravate acne. Of the second generation progestins ethynodiol diacetate, norethindrone and levonorgestrel have the lowest androgenic activity. Of the third generation progestins, desogestrel, norgestimate and gestodene have the lowest intrinsic androgenic activity.

The triphasic combination oral contraceptive norgestimate ethinyl oestradiol (orthotricyclene) was the first low dose oral contraceptive to receive Food and Drug Administration approval for the treatment of acne in the United States.

Adverse effects of oral contraceptives: The most common adverse effects associated with oral contraceptives are nausea, breakthrough bleeding, weight gain and breast tenderness.

Rare serious adverse effects include hypertension, thrombophlebitis and pulmonary embolism. There is controversy in the literature as to whether there is an increased risk of venous thromboembolism associated with oral contraceptives containing desogestrel and gestodene. The risk of myocardial infarction, however, may be lower in women using these oral contraceptives compared to those containing a second generation progestin.

The issue of possible contraceptive failure while on antibiotics and oral contraceptives is under debate. A large review concluded that available scientific and pharmacokinetic evidence does not support the hypothesis that antibiotics (with the exception of rifampicin) lower the contraceptive efficacy of oral contraceptives (Archer and Archer, 2002).

Antiandrogens

Cyproterone acetate is an antiandrogen that blocks the androgen receptor. It is available in

Europe and Canada as the oral contraceptive Dianette (cyproterone acetate 2 mg combined with ethinyloestradiol 35 μg). This is widely used in Europe for the treatment of acne (Greenwood et al, 1985).

Cyproterone acetate alone has also been used to treat acne. Trials have demonstrated improvement in 75–90% of acne patients prescribed cyproterone acetate 50–100 mg daily with or without ethinyloestradiol (Hanstead and Reymunn, 1982).

Side effects of cyproterone acetate include menstrual abnormalities, breast tenderness, nausea, vomiting, fluid retention, headache and melasma. It has also been associated with liver dysfunction and rarely blood clotting disorders. Pregnancy should be avoided during therapy because of the potential for feminization of the male fetus.

Spironolactone

Spironolactone acts as an androgen receptor blocker and inhibits 5-alpha reductase. In doses of 50–100 mg twice daily it reduces sebum production and improves acne. The starting dose should be around 25–50 mg twice daily and providing the patient does not experience any breast tenderness or headaches can be increased to the maximum 100 mg twice daily. As an antiandrogen, there is a risk of feminization of the male fetus if spironolactone is taken by pregnant women (Hughes and Cunliffe, 1988).

Spironolactone can be combined safely with the oral contraceptive in sexually active females to avoid the risk of pregnancy and feminization of the male fetus.

Response to acne and sebum reduction takes 3–6 months with all hormonal therapies.

ORAL ISOTRETINOIN

Oral isotretinoin is recommended for severe acne (*Figure 3*) and is effective as it reduces hypercornification, lowers sebum excretion, has anti-inflammatory effects and leads to a reduction in *P. acnes* (Cunliffe and Stables, 1996). Isotretinoin is a lipid-soluble drug hence its absorption is enhanced when administered with food. Once absorbed it is rapidly and widely distributed and binds to tissue proteins. There is no progressive accumulation in skin or subcutaneous fat, or long-term retention in the sebaceous glands. Within 3 weeks of discontinuation, no detectable retinoid remains, hence the sustained improvement in acne cannot be explained by persistence of the drug. Over recent years, dermatologists have increasingly used this drug to treat acne that has not responded to more conventional therapy (*Table 2*). However, these indications remain outside the current product licences.

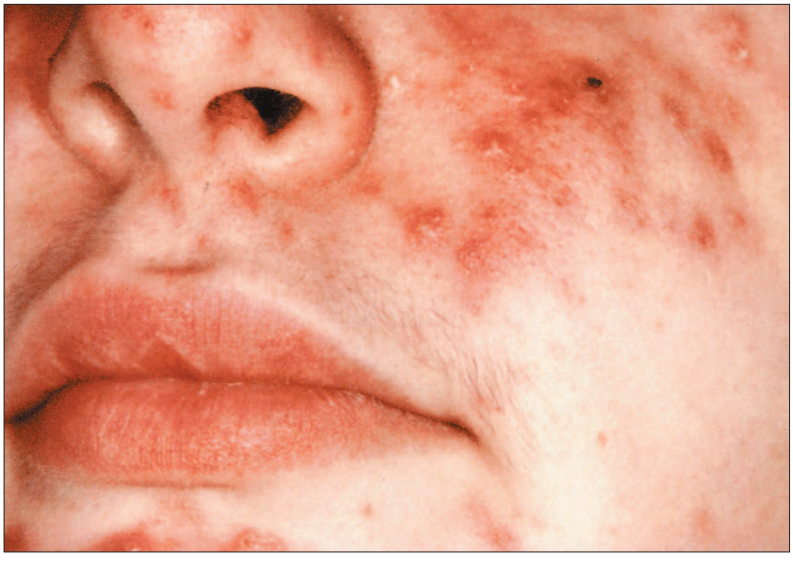

Figure 3. Severe acne.

Dosage regimens of isotretinoin for acne

Isotretinoin has been available for use in acne since the 1980s. Dosage regimens vary from 0.1–2.0 mg/kg/day but doses >1.0 mg/kg/day are rarely used for acne as side effects tend to limit tolerance (DiGiovanna, 2001). It has being suggested that cumulative dose is important in preventing relapse and studies have suggested that a cumulative dose of 120–150 mg/kg is associated with a lower relapse rate that lowers cumulative levels. However, further studies are required to confirm this. The manufacturers recommend the starting dose for acne is 0.5 mg/kg/day. This should be taken with food as a single or divided dose. Using a low starting dose (0.5 mg/kg/day or less) reduces the likelihood of initial acne flare. The dose can be gradually increased according to side effects and clinical response.

Monitoring while on oral isotretinoin

A careful medical history is required before prescribing isotretinoin to exclude pre-existing disease which might be associated with hyperlipidaemia, renal or liver abnormalities.

The following monitoring advice is based on the consensus meeting that took place at the European Academy of Dermatovenereology in

TABLE 2.
Indications for the use of oral isotretinoin

Ideally reserved for	Severe acne
In carefully selected cases with a combination of the following	Moderate acne unresponsive to conventional therapy
	Moderate acne relapsing after conventional therapy
	Acne scarring
	Psychological effects resulting from acne and scarring
	Unusual forms of acne

1997 (Cunliffe et al, 1997). Baseline measurements should include pre-therapy urea, electrolytes and creatinine, liver function tests, fasting blood lipids, urine pregnancy test for all females of childbearing age and blood sugar (if family history of diabetes or indication in a patient's history). Providing baseline investigations are normal and there are no predisposing medical problems, frequent biochemical monitoring throughout therapy is not considered mandatory and it was suggested that this should be left to the discretion of the prescribing physician. However, the pharmaceutical companies still suggest liver function tests and fasting lipids should be monitored at least once during therapy and most clinicians elect to follow this recommendation.

In females a negative pregnancy test should ideally be obtained 2–3 days before menstruation and the drug should then be started on the second or third day of the menstrual cycle. Recommendations for prescribing isotretinoin in females of childbearing age are shown in *Table 3*. Regular (monthly) pregnancy testing throughout treatment and 1 month post therapy is currently being considered by the European Harmonisation Programme and may well be enforced in April 2004.

TABLE 3.
Recommendations for prescribing oral isotretinoin in females of childbearing age

Signed consent should be obtained, confirming that the patient knows not to get pregnant while on therapy and for 4 weeks after the end of therapy
Pre-treatment pregnancy test is required
Commence treatment on the second or third day of menstruation
Ensure reliable contraception where necessary
Potential monthly pregnancy testing throughout treatment being currently considered and possibly advocated from April 2004 in line with the European Harmonisation Programme

TABLE 4.
Potential interactions of oral isotretinoin with other drugs

Drug	Effect
Alcohol	Heavy intake of alcohol reduces efficacy of oral isotretinoin and may increase risk of hepatotoxicity
Imidazole	Antifungals may increase blood levels of isotretinoin
Highly acidic drugs	For example, salicylic acid and indomethacin have a high affinity for albumin and may displace isotretinoin from leaving sites, leading to an increase of drug concentration in the plasma
Carbamazepine	Plasma levels decrease when concurrent isotretinoin is taken
Oral tetracycline	Both isotretinoin and tetracyclines can lead to raised intracranial pressure. There are reports of intracranial hypertension in patients treated with both drugs
Vitamin A	Vitamin A and retinoids produce additive toxic effects

Drug interactions on oral isotretinoin

Oral isotretinoin is metabolized by cytochrome P450 enzymes, which are inducible by some drugs and inhibited by others. The clinical relevance of such potential interactions are not always clear. *Table 4* outlines some potential interactions.

Adverse effects of oral isotretinoin and their management

Mucocutaneous side effects including dryness of skin and mucus membranes are almost universal in all patients receiving retinoids. They are dose related, predictable and easily managed with emollients and false tears (Mergel, 1997).

Myalgia and muscle stiffness occurs in up to 16% of patients, particularly those participating in heavy exercise. In rare cases raised creatinine kinase has been demonstrated. The patient should be advised to avoid taking strenuous exercise.

Hepatotoxicity is a very rare idiosyncratic reaction which is seen on isotretinoin. Abnormalities are most likely to occur in the context of heavy alcohol intake and therefore alcohol consumption should be minimized or stopped during isotretinoin therapy.

Hyperlipidaemia is one of the most common acute adverse effects during synthetic retinoid therapy. The increase in serum triglyceride and cholesterol is proportional to the dose of the drug and reverses within 4–8 weeks of stopping the retinoid. Retinoid-induced hyperlipidaemia occurs more frequently in patients with underlying predisposing factors, e.g. obesity, alcoholism, diabetes and familial hyperlipidaemia. Pre-treatment levels are not necessarily predictive of increased lipids during therapy. Increased levels of triglycerides and cholesterol during retinoid treatment can be managed at least partially by an appropriate diet and supplementation with fish oil capsules. Severe hypertriglyceridaemia >10 mmol/litre may be associated with eruptive xanthomas and acute pancreatitis.

Pseudotumour cerebri and benign intracranial hypertension with papilloedema is a rare complication of isotretinoin therapy and has been reported when oral isotretinoin has been combined with oral tetracyclines. The reaction is likely to be an independent idiosyncratic effect from either drug but manufacturers advise against combining these agents.

Depression and suicide have been reported as a possible adverse event of isotretinoin (Hazen et al, 1983), while acne itself is often associated with anxiety and depression. Prescribers should be aware that oral isotretinoin is frequently used in a vulnerable age group and there may be a small number of cases that develop depression

while on isotretinoin (Drug and Therapeutics Bulletin, 2003). Clinicians should be vigilant about this when reviewing their patients.

Impaired nocturnal vision has been reported in a small proportion of patients receiving isotretinoin. This appears to be reversible in the majority but care should be used when prescribing isotretinoin for those who drive at night or are pilots. *Figure 4* demonstrates the mechanism for night blindness.

Isotretinoin is a known teratogen and is absolutely contraindicated in pregnancy. Careful counselling is mandatory and patients should be informed and should consent not to get pregnant while on therapy and for 4 weeks post treatment.

Oral isotretinoin is a highly effective therapy for severe acne.

CONCLUSIONS

Moderate to severe acne merits the use of systemic therapies as outlined in this article. Oral antibiotics remain an important therapeutic modality but antibiotic usage policies should be considered. *P. acnes*'s resistance has been recognized as an emerging problem and awareness of this concept should be considered. Oral isotretinoin is a very useful treatment for those patients with severe acne or in certain selected cases for which antibiotic or hormonal therapy are not appropriate or have been unsuccessful. Considering the adverse effects, vigilance and monitoring are necessary. HM

Figure 2 *is published by kind permission of Professor WJ Cunliffe and Dr A Eady.*
Conflict of interest: none.

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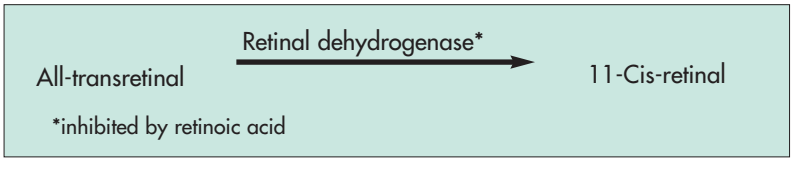
Figure 4. Mechanism for night blindness.



KEY POINTS

- Systemic treatments should be aimed at aetiological factors implicated in acne vulgaris.
- Systemic antibiotics remain the mainstay of therapy for moderate to severe acne in the first instance.
- Antibiotic resistance to *Propionibacterium acnes* can result in reduced efficacy of treatment in some patients.
- Hormonal therapies remain an option for female patients with acne.
- Oral isotretinoin should be reserved for patients with severe acne where possible but in certain cases may be useful in those with moderate to severe disease where they have relapsed or failed to respond to adequate alternative therapies and/or have additional or significant scarring as a result of their acne.
- It is important to be aware of potential adverse effects when using systemic therapies for acne.