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Isotretinoin for the management of acne

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Dr Marius Rademaker

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In recent years he has been involved in a number of single and multicentre clinical trials of dermatological agents (itraconazole, liarazole, amorolfine, terbinafine, griseofulvin, ciclopirox, 5-fluoruracil, melanoma vaccine, topical retinoids, isotretinoin), as well as developing new models of dermatology healthcare delivery. He sits on the editorial board of the Australasian Journal of Dermatology, is a reviewer for British Medical Journal, Clinical and Experimental Dermatology, Contact Dermatitis, Lancet, New Zealand Medical Journal and Paediatric Dermatology, as well as for the Cochrane Dermatology Group.

Abbreviations used in this review
CRH = corticotrophin-releasing hormone
GI = glycaemic index
IGF = insulin-like growth factor
IL = interleukin
MMP = matrix metalloproteinase
PCOS = polycystic ovary syndrome
RAR = retinoic acid receptors
RARE = retinoic acid response elements
RXR = retinoid X receptors
TLR = Toll-like receptor
TNF = tumour necrosis factor

This publication summarises two recent presentations by Dr Mark Tang from the National Skin Centre in Singapore, and Professor Marius Rademaker from Hamilton, NZ. They spoke about the use of isotretinoin for the management of acne at a meeting 'Isotretinoin: New safety information & individualised dosaging – what 30 years has taught us' in Hong Kong in September 2012.

ACNE – NEW INSIGHTS AND UPDATES

Dr Mark Tang, National Skin Centre

Acne vulgaris is a highly prevalent and clinically significant problem that affects up to 80–90% of adolescents. In the short term, it is associated with significant social and psychological impacts in patients.[1] In the longer term, it can result in permanent scarring that many patients spend a lot of time, effort and money to reverse. Interestingly, it has been shown in one Hong Kong study that the clinical severity of acne does not necessarily correlate with the impact on the quality of life of patients.[2] The same study showed that predictors for acne disability include female sex, high stress levels and willingness to pay more for a cure.

Pathogenesis

Acne is a chronic inflammatory disease of the pilosebaceous unit that results from the following four key pathogenic factors: i) increased sebum secretion; ii) follicular occlusion; iii) *Propionibacterium acnes*; and iv) inflammation. Research has shown a genetic basis for acne, particularly a maternal history of acne being associated with early acne onset, increased comedones and greater relapse rates.[3,4]

Genetic or intrinsic factors

Recent studies have also increased our understanding about sebaceous gland activity and sebum production. We now know that sebum production by the sebaceous gland can be influenced by many different hormones and neuromediators such as androgens, IGF, CRH, melanocyte-stimulating hormone and substance P, which, in turn, can be influenced by stress, diet and hormonal changes.

Another recent insight is that some patients with acne are genetically prone to develop an 'exaggerated' inflammatory response to *P. acnes*, the key pathogen involved in acne vulgaris. For instance, patients with SAPHO or PAPA syndrome experience fulminant acne, fever, joint pain and pustulosis due to an underlying autoinflammatory condition characterised by enhanced immunological reactions to *P. acnes*, defective apoptosis and increased IL-8 and TNF-α levels. In addition, new genetic mutations have been identified in patients with acne inversa or hidradenitis suppurativa, which lead to follicular occlusion and immune dysfunction that are responsible for this debilitating condition.

Environmental factors

The role of food in the pathogenesis of acne has been controversial. Recent epidemiological studies have suggested that a Westernised diet may play a contributory role.[5] This relationship of food and acne has been linked to increased IGF secretion, which can directly stimulate lipid production in sebocytes and keratinocyte proliferation, leading to follicular occlusion. It has also been shown that IGF-1 gene polymorphism increases the risk of severe acne. High IGF levels are stimulated by the intake of high-GI foods. A recent study by Kwon et al showed that a low-GI diet for 3 months led to a reduction in acne lesions as well as sebaceous gland activity on biopsy.[6] Stress has been shown to aggravate acne. This is especially relevant in adolescents taking stressful exams, as seen in a Singapore study.[7] The effect of stress on acne has been linked to CRH secretion, which can directly stimulate the pilosebaceous unit.

Much progress has also been made in our understanding of how *P. acnes* causes inflammation in acne. *P. acnes* can not only initiate inflammation via the innate immune system via TLRs, it can also directly release inflammatory mediators such as lipases and proteases, as well as cytokines such as IL-1α, IL-8 and TNF-α, which further worsen the inflammation. In addition, *P. acnes* can lead to host cell destruction and scarring via the release of MMPs. Finally, *P. acnes* also has the ability to exist as biofilms, which can perpetuate antibiotic resistance. *P. acnes* resistance is increasing globally, with up to 50% of isolates being resistant to at least one antibiotic.[8] *P. acnes* resistance was seen more often in older patients and those with longer disease duration.

Clinical implications

Armed with these new insights, clinicians must target each of the four key pathogenic factors (Figure 1) to effectively treat acne. Clinicians also need to have a long-term perspective when treating acne, which is a chronic relapsing condition. Of the various options available in our armamentarium for treating acne, isotretinoin is the only one that effectively targets all four of the key pathogenic factors.

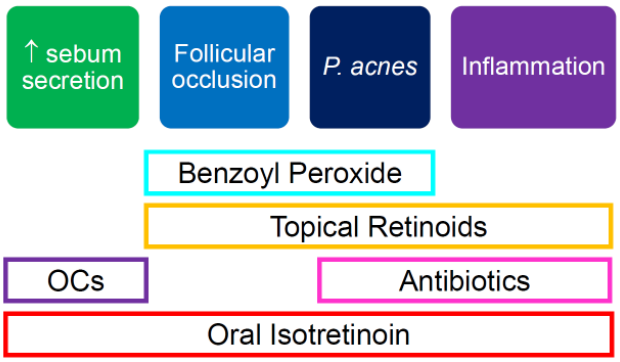

Figure 1. Acne treatments according to key pathogenic factors of the disease targeted

First-line topical treatment for acne includes retinoids, which target the microcomedone and abnormal desquamation, and reduce inflammation by inhibiting TLRs and decreasing MMP levels. Benzoyl peroxide should also be applied, due to its ability to prevent *P. acnes* resistance. The new combinations of benzoyl peroxide with retinoids or antibiotics are useful options.

Oral treatments include oral antibiotics, oral contraceptives and isotretinoin. Antibiotics are given for 3–6 months, mainly for their anti-inflammatory effects. Adverse effects need to be considered, particularly drug allergies such as Stevens-Johnson syndrome, with the use of trimethoprim/sulfamethoxazole (Bactrim).

New insights into isotretinoin

Recent studies have shown that isotretinoin (13-*cis* retinoic acid) not only has effects on the pilosebaceous unit, but also has immunoregulatory effects, such as decreasing TNF-α and interferon-γ levels, decreased monocyte TLR-2 expression and the inflammatory response to *P. acnes*.[9,10] In a recent 4-year retrospective analysis of the use of isotretinoin in 2255 patients at the National Skin Centre in Singapore, oral isotretinoin was found to be effective and safe.[11] The three key findings were that: i) isotretinoin was safe and effective; ii) a low isotretinoin dose worked well; and iii) isotretinoin was overall extremely well tolerated with a low incidence of liver and lipid derangements. Abnormalities in liver aminotransferases were seen in <3% of patients, with males, patients aged ≥25 years and those with a history of viral hepatitis being at increased risk. Mild increases in triglyceride and LDL cholesterol levels were seen in 4.8% and 12.1% of patients, respectively, with males, patients aged ≥25 years and those with a positive family history of dyslipidaemia being at increased risk. Complete remission was seen in 94%, and it was more likely in patients who had received a cumulative isotretinoin dose of ≥100 mg/kg.

In terms of therapeutic use, there is a trend to use lower daily doses of isotretinoin, which is associated with less initial flares and improved patient satisfaction. Lower isotretinoin doses reduce the safety concerns of dose-related side effects.

There are many treatment options available for acne, including a number of light or laser devices. However, clinicians need to differentiate between evidence-based science and marketing hype. It is also important to understand that 'FDA approval' for devices does not equate to clinical efficacy.

Take home points

Acne
• Not just a cosmetic or adolescent problem
• We have a better understanding of its genetic and molecular basis
Treatment strategy
• Treat early and target the key pathogenic factors
• Maintain treatment until remission
Treatment options
• Keep it simple to improve compliance
• Use antibiotics judiciously to prevent resistance
• New insights into acne pathogenesis provide new treatment options

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PERSISTENT, RESISTANT OR UNRESPONSIVE: INDIVIDUAL DOSAGING OF ISOTRETINOIN

Prof Marius Rademaker, Hamilton, NZ

Changes in acne treatment

The perception of acne has changed over the years, from being an adolescent problem in the 1980s to affecting all age groups now, with half of European women aged 25–60 years being affected by the condition. This probably reflects changes in diet, with more high GI foods and greater calories consumed. Our understanding of the pathogenesis of acne has also developed, from being considered purely due to excess sebum prior to 1980 to being regarded as an autoimmune disorder triggered by an inflammatory response to *P. acnes*.

There is some increase in sebum production in acne, but it is not actually that much and can be quite variable. What is more important is the alteration in sebum composition, with it becoming stickier and more inflammatory. Also, while overgrowth of *P. acnes* is seen, it is also not that much, and there is no consistent correlation between the number of these bacteria and disease severity. What is important is an individual's genetics in determining the immune inflammatory response to *P. acnes*. Inflammatory products of *P. acnes* include TNF-α, IL-1β and IL-8, which are the types of cytokines also seen in psoriasis and eczema. As such, acne should be regarded as a chronic autoimmune disease with a time course of 5–10 years, rather than several months as previously believed. This

has important implications for our approach to its management, and early aggressive management may be appropriate, especially with increasing concerns associated with long-term antibiotic use. It is also important to remember that patients expect 100% clearance with their treatment.

Isotretinoin

Isotretinoin is a naturally occurring retinoid that was first developed in 1955 for psoriasis, but it was relatively ineffective so interest was lost. A few years later, research interest was rekindled as a potential treatment for cancer, keratinising disorders and acne. Isotretinoin was first reported to be effective for acne in 1979,[1] and was approved in 1982.

Oral isotretinoin is absorbed in the gut, stored in the liver and then delivered to skin cells and stored in the reticuloendothelium from where it is transported to the nucleus. In the nucleus, retinoids bind to RAR and RXR, which are bound to RARE on DNA (Figure 2). Retinoids cause conformational changes to repressor proteins that are also bound to DNA, resulting in gene activation. These direct effects are important in differentiation, but retinoids also have indirect effects that downregulate genes without interacting with RARE. These indirect effects include: i) inhibition of the activity of other transcription factors (e.g. AP-1, NF-IL6) that stimulate MMPs; and ii) competition for commonly acquired co-activator proteins.

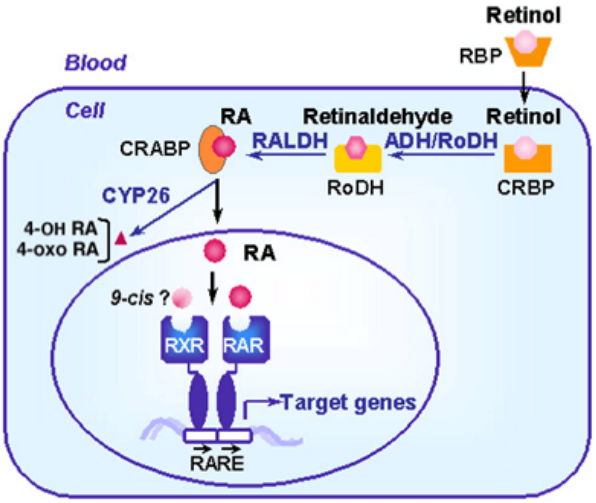

Figure 2. Intracellular pathways involved in the actions of retinoids

There are three subtypes of retinoid receptors (α, β, γ) and several isoforms (α1, α2, β1, β2, β3, β4, γ1, γ2), each of which is encoded by distinct genes whose expression is tissue specific. By understanding the biology of retinoids, their potential value can be realised. The nuclear retinoid receptors normally act as heterodimers (one RXR and one RAR), but they can also act as homodimers (2 × RXRs). They can also bind to vitamin D receptors, thyroid hormone receptors, liver X receptors and peroxisome proliferator activate receptors (which are very important in diabetes). The main ligands for RAR and RXR are all-*trans* retinoic acid and 9-*cis* retinoic acid, respectively. While 13-*cis* retinoic acid (isotretinoin) does not bind to either receptor with any appreciable affinity, it is reversibly metabolised to all-*trans* and 9-*cis* retinoic acid.

Effects of isotretinoin

Isotretinoin has immunomodulatory, anti-inflammatory, anticancer and antiangiogenic effects (Figure 3). The clinical effects of retinoids in general are mediated by >500 genes that have a variety of effects, with 311 known to be upregulated and 212 downregulated. In the classic RAR/RXR-RARE pathway, 27 genes are mediated (26 upregulated) while 100 genes are mediated in RAR-RXR pathways without RARE. Among these, there is a 2-fold increase in genes affecting collagen with 8 weeks of isotretinoin therapy, and a 6-fold reduction in genes that induce steroid dehydrogenase. Furthermore, the effects of isotretinoin, given at the right dose for the right duration, are biphasic (Table 1). This biphasic pattern manifests as initial induction of apoptosis and cell cycle arrest within the sebaceous gland, followed by a pattern of wound healing with subsequent substantial cell repair and remodelling.

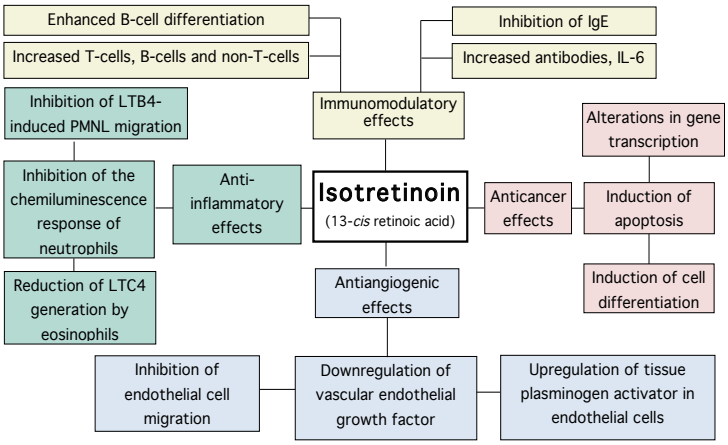

Figure 3. Summary of the clinical effects of isotretinoin

	Week 1	Week 8
Upregulation	Tumour suppressors Protein processors Genes involved in transfer or binding of ions and small molecules	Structural proteins (e.g. collagen, fibronectin)
Downregulation	–	Steroid, cholesterol and fatty acid metabolisers

Table 1. General effects of isotretinoin at weeks 1 and 8

Isotretinoin results in significant cell cycle arrest, apoptosis and decreased DNA synthesis in the sebaceous gland, and these result in alteration in differentiation of basal sebocytes, a 90% decrease in the size of the sebaceous glands and decreases in proliferation and sebum production. Sebocyte apoptosis can also eliminate the stem cells; however, this is dose dependent, probably occurring at isotretinoin dosages ≥1 mg/kg/day. When stem cell elimination occurs, there is a prolonged effect on sebocytes, with patients experiencing long-term or permanent effects (e.g. dry lips/eyes) due to nonrecovery of the sebocytes many years after receiving isotretinoin therapy. Stem cells are retained with lower doses (e.g. 0.1 mg/kg/day), and sebocytes are able to recover.

Isotretinoin promotes proliferation of normal epidermis via shortening of the mitotic phase of the cell cycle, normalising hyperproliferative epithelia and altering terminal keratinocyte differentiation. Effects of isotretinoin on the epidermal lipids include decreases in wax esters, squalene and glyceride fraction, and increases in cholesterol (relative), free sterols and total ceramides.

Summary of clinical effects of isotretinoin

- Isotretinoin affects >500 genes
- The effects are time and dose dependent
- At lower doses:
  - stimulates a healing pattern of gene expression
  - reduces the inflammatory/autoimmune response of *P. acnes* to sebum
- At higher doses:
  - causes apoptosis of sebocyte stem cells

Isotretinoin pharmacokinetics

Oral isotretinoin is absorbed in 30–60 minutes (doubled when taken with food). It reaches peak concentration in 2–4 hours, and its elimination half-life is 10–20 hours. This means isotretinoin is completely eliminated from the serum within 3–5 days, but it can stay in the epidermis for 2–4 weeks. The traditional indications for isotretinoin are: i) severe nodulocystic acne at a dosage of 0.5–10 mg/kg/day for 4–5 months (cumulative dose 120–150 mg/kg), and this has worked very well for the last 30 years; ii) moderate acne (grade 1.5–4.0) that has responded poorly to antibiotics; and iii) mild acne (grade 0.5–1.5) with scarring that has responded poorly to 6 months of treatment.

Isotretinoin dosing

The traditional dosage of isotretinoin is 1 mg/kg/day, but experience has shown that this high dosage is now considered unnecessary. The original dosage was 2 mg/kg/day

in 1970 for cancer.[Peck 1] As early as 1980, lower dosages (e.g. 0.05–0.1 mg/kg/day, 2.5mg three times weekly) have been shown to provide similar degrees of improvement in similar timeframes as higher dosages (see Table 2).[2–6] There are also many other studies that have shown the effectiveness of low dosages, and combined they paint a picture of no evidence of a dose response in the 0.1–2 mg/kg/day range.

Study	Number of patients	Isotretinoin dos(ag)es	Main Results
Farrell (1980)[2]	14	0.1, 0.5, 1.0 mg/kg for 12wk	Clinical improvement in all groups
Jones (1983)[3]	10	0.1, 0.5, 1.0 mg/kg for 4mo	Equal clearance in all groups – sustained for a further 16wk
Palmer (2004)[4]	8	20mg, 1 or 2×wk	Clearance in all participants (all had 2–4 relapses on conventional isotretinoin; none wished to discontinue study treatment)
Geissler (2003)[5]	11	5 mg/d, 2 mg/d, 2.5mg 3×wk for 6mo	Good results for all patients
Plewig (2004)[6]	28	10, 20 mg/d for 6mo	~85–90% decreases for both inflammatory and noninflammatory lesions

Table 2. Studies of isotretinoin for acne showing dose-independent responses

A double-blind placebo-controlled study was conducted in NZ in 60 patients treated with isotretinoin 5 mg/day or placebo for 4 months, then 4 months of open-label isotretinoin, followed by 2 months of follow-up with no treatment.[Rademaker] Isotretinoin was associated with a significant reduction in acne lesions of >50% during the 4 months of the placebo-controlled phase, while placebo was not. During the open-label phase, the isotretinoin arm continued to experience improvements (with many patients achieving complete remission), while placebo recipients who had started open-label isotretinoin also experienced a reduction in lesions (see Figure 4).

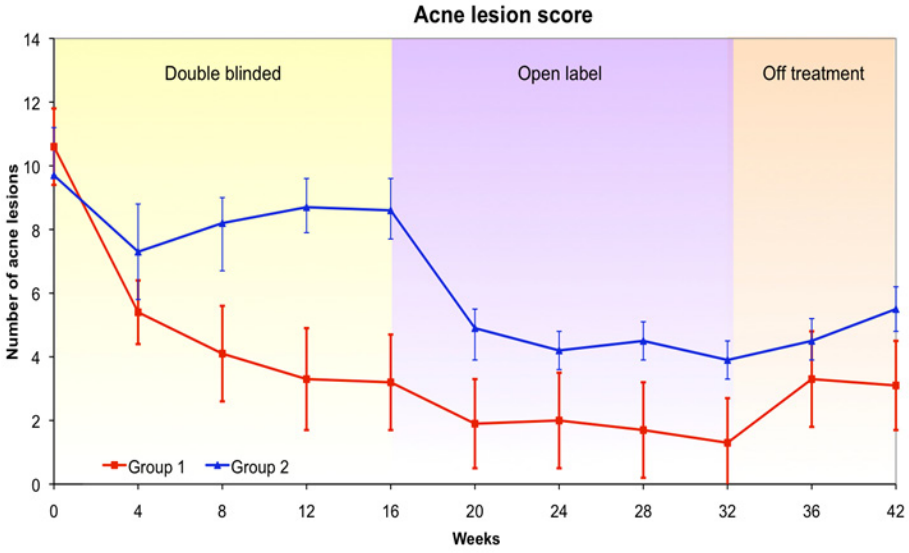

Figure 4. Effects of isotretinoin 5 mg/day on number of acne lesions[7]

It is now clear that acne can be cleared with isotretinoin 5 mg/day or 10mg three times per week (Table 3). At this isotretinoin dosage, total clearance can be expected without compromising the rate of response, regardless of severity. While 2 mg/day is considered to be the lower end of the effective oral dose, it is generally not recommended due to variability caused by food intake.

Patient group	Initial	Maintenance
Adolescent girls	10 mg/d for 2–3mo	10mg × 3/wk for 9–10mo
Adolescent boys	10 mg/d for 4mo	10mg × 3/wk for 8mo
Adults	10 mg/d for 3mo or 5 mg/d*	10mg × 3/wk for 1–2yr or 5 mg/d* for 1–2yr
*The availability of the 5mg dose enables once daily dosing, which patients often find easier to remember than alternate days, and reduces adverse effects		

Table 3. Isotretinoin dosing

Treatment failure

The primary failure rate (not early relapse) of isotretinoin is 1–2%, and is not dose dependent. Many apparent failures are just patients who are slow responders who may need to be treated for 12–18 months. Predictors of slow response include smoking, missed macrocomedos, age <14 years, excessive seborrhoea and truncal acne, but responses can be improved as follows.

- Smokers should be advised to stop smoking and be treated for 1–2 years; adding trimethoprim 300 mg/day can also help.
- Continuing treatment for 12–18 months is recommended for managing macrocomedos, but acne surgery may also be indicated.
- Additional hormonal treatment should be considered for patients with PCOS.
- Trimethoprim can be added for younger patients (or just wait for them to get older).
- Increasing the isotretinoin dosage to 20 mg/day (occasionally 1 mg/kg/ day for the first 1–2 months) to increase the degree of apoptosis may be appropriate for patients with seborrhoea. Adding benzyl peroxide, a topical retinoid and UV light or photodynamic therapy may also be appropriate for these patients.
- Treat patients with truncal acne for ≥6 months, and add trimethoprim 300 mg/day or another anti-inflammatory antibiotic.

Relapse and cumulative dosing

The dogma is that you need a cumulative isotretinoin dose of 120–150 mg/kg to prevent relapse. Relapse is a secondary failure of treatment. However, there is no physiological basis for this; cumulative dose is not used in assisting treatment decisions for any drug besides isotretinoin. One issue is the definition of relapse, which can be very subjective. For some relapse is defined when the treating physician believes a further course of isotretinoin is required.

Cumulative dose is a function of both daily dose and duration of treatment. Most older studies of isotretinoin have generally only compared different daily doses over the same fixed 4-month treatment period. However, it is the time that sebaceous gland activity is suppressed that determines whether a patient will relapse or not, not the time he/she is receiving medication. The first few studies of isotretinoin (that used 1–2 mg/kg/day and very high cumulative doses) still had relapse rates in the 30–50% range.[1,8] Two long-term studies of isotretinoin for acne with follow-up periods of 5 years have reported relapse rates. One of these found that about 17% of patients (n=299) required two isotretinoin courses, 5% required three, and 1% required four or five.[9] Predictors of relapse in this study were severe acne, female aged >25 years and prolonged acne history. The second study of 218 patients who received isotretinoin 0.1–1.0 mg/kg/day for 8 months found relapse rates at 1, 3 and 5 years of 14%, 40% and 49%, respectively.[10] However, it is likely that the 5-year relapse is probably more a reflection of the natural history of chronic acne, rather than being related to isotretinoin therapy. Predictors of relapse in this study were age and acne severity, but not daily or cumulative dose. Similarly, daily and cumulative doses were not predictors for relapse in a prospective study reporting a 52% relapse rate in 52 patients who received isotretinoin 0.3–1.0 mg/kg (cumulative 108–180 mg/kg); predictors of relapse included post-treatment seborrhoea,

acne severity, young age, family history and truncal acne.[11] Overall, factors important in relapse include incomplete acne clearance (arguably not technically 'relapse'), macrocomedonal acne, hyperandrogenism, young age and being a female aged >30 years with late-onset acne, while factors such as daily or cumulative dose, family history, truncal acne, male sex, etc. are not important.

As isotretinoin 1 mg/kg/day is associated with apoptosis of sebaceous glands and stem cells, sebum is suppressed for 3–6 months after discontinuation of treatment. In contrast, isotretinoin 0.1 mg/kg/day is associated with less apoptosis of sebaceous glands and no or minimal stem cells, so sebum suppression probably persists for only 3–6 weeks after treatment. This means that 6 months of the higher dosage is equivalent to about 1 year of the lower dosage in terms of sebum suppression, even though the respective cumulative doses are quite different.

Summary of relapse

- Relapse incidence
  - Expect 20–25% of patients to relapse, of who 5% will need a third course and 1% will need a fourth
  - Expect 50% of patients aged <14 years to relapse
  - Expect ≥30% of women aged >25 years to want to go back onto treatment
- Relapse prevention
  - Ensure that acne has completely resolved
  - Treat for a further 4–6 months
  - Use isotretinoin 5 mg/day or 10mg × 2–3/week
  - Ensure any macrocomedos have resolved
  - Ensure PCOS is treated
  - Stop smoking

Current isotretinoin use

Prof Rademaker noted that he currently uses isotretinoin for the first-line treatment of nodulocystic acne, moderate acne and mild acne, and as second-line therapy for negligible acne if response has been poor with 3 months of other treatments based on the rationale that no degree of acne is unimportant to the patient. While physicians may consider almost complete clearance a good result, a patient is unlikely to be satisfied until complete clearance has been achieved, and therefore that should be the goal of therapy.

Isotretinoin is also Prof Rademaker's first-line choice for acne in the following patient groups.

- **Inflammatory bowel disease**: there is no association between isotretinoin use and Crohn's disease, and isotretinoin has a lesser association with ulcerative colitis than minocycline. While isotretinoin can cause proctitis, resulting in worse symptoms of ulcerative colitis, this is only seen with higher dosages (e.g. 1 mg/kg/day), whereas acne can be effectively treated with lower dosages (e.g. 10 mg/day). Moreover, the anti-inflammatory effects of low-dose isotretinoin are similar to those of azathioprine, and low-dose isotretinoin for acne may improve symptoms of inflammatory bowel disease.
- **Systemic steroid/immunosuppressant recipients**
- **Depression/anxiety**: patients with these conditions often do better with isotretinoin than with selective serotonin reuptake inhibitor therapy, as acne is often a significant contributor to depression and anxiety.
- **Persistent adult acne**, particularly women aged >35 years, who are very unlikely to be happy with the prospect of applying long-term topical agents.
- **Infantile acne with scarring**: the risk of premature epiphyseal closure with isotretinoin in children aged <12 years needs to be considered and discussed, but this has only been reported with very high dosages (2 mg/kg/day).
- **Comedonal acne**: treatment duration needs to be 12–18 months
- **Acne scarring**: low to very low dose very effective for active or recent scarring

Combination treatments

When isotretinoin is insufficient on its own, it can be combined with other treatments as follows.

- **Trimethoprim** 300 mg/day for 2–3 months can be added for inflammatory acne, Gram-negative folliculitis and slow responders or smokers after 3 months of isotretinoin; erythromycin is usually avoided due to adverse effects and resistance. Beware of the risk of toxic epidermal necrolysis.
- Low-dose **minocycline** (50mg and isotretinoin 5–10 mg on alternating days) can be added when rosacea is present.
- **Hormonal therapies** (Estelle 35 [cyproterone acetate/ethinyloestradiol], flutamide, spironolactone, metformin) can be added for PCOS, hyperandrogenism, female slow responders and female fast relapsers.
- **Prednisone** 0.5 mg/kg/day for 2–4 weeks than tapered over 4–12 weeks for very inflammatory acne, cystic acne, acne fulminans and pyoderma faciale.
- **Surgery** (dermabrasion, electrodessication) for microcomedones and acne scars. The more traditional thinking that surgery should not be used within 6–12 months after isotretinoin is based on destruction of sebaceous gland stem cells seen with higher doses and the consequent lack of recovery. However, with the very low doses of isotretinoin now recommended, surgery can be performed within a few days of stopping isotretinoin, and isotretinoin restarted a few weeks after surgery may actually help with healing.
- **Laser** for rosacea, acne scarring and postinflammatory pigmentation. Intense pulsed light (IPL), pulsed dye laser (PDL) and Fraxel CO_2 laser therapies are all safe.

Adverse effects

Transient adverse effects associated with isotretinoin 5mg include dry lips during the first 4 weeks and actinic cheilitis, for which the use of sunscreen on the lips is indicated throughout treatment. Isotretinoin at any dosage should never be used in pregnancy. While there does not appear to be any association between isotretinoin 5mg and mood changes, it cannot be excluded.

Take home points

Major changes to patients' perceptions of acne have occurred over the last few decades
Patients expect 100% clearance
Low-dose isotretinoin (5 or 10 mg/day) • Provides equivalent sebum suppression as 1 mg/kg/day (with lower cumulative dose) • Does not cause apoptosis of stem cells • Is useful a wide range of acne severities and patients • Can be used with other treatments • Well tolerated

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Douglas Dermatology commissioned independent specialist firm Oliver Henry Consulting, to conduct market research into acne patient profiles and treatment regimens in Hong Kong. The research included in-depth interviews with certified dermatologists and dermatology specialist GPs. The research was conducted in January 2012 and highlights included:

- Patient numbers with acne may not be increasing dramatically, but patients are presenting earlier to dermatologists, often after having tried to self-medicate, or seeing a GP

  "Most of them would have purchased treatment from over-the-counter. Those are usually with mild acne problem. The moderate and severe acne patients that present to me would have visited the GP before, but they are unable to control their acne problem." – Doctor Quote

- Lack of efficacy of previously used products and an increasing awareness of image are driving patients to see dermatologists.

  "It's because they failed in previous treatments and I am a specialist. They believe that I can help them. They feel that acne has an impact on their appearance and quality of life." – Doctor Quote

- The use of combination therapy in acne treatment is prolific. Dermatologists treat over 70% of patients, on average with combinations of benzoyl peroxide, topical/oral antibiotics, topical retinoids and isotretinoin. The latter, oral isotretinoin, is the most commonly used monotherapy

  Combination therapy results in higher costs and a variety of side effects, due to multiple products, along with lower patient compliance, especially when multiple formulations are involved.

- Isotretinoin is the only treatment considered as a cure for acne; with high success rates and low recurrence rates.

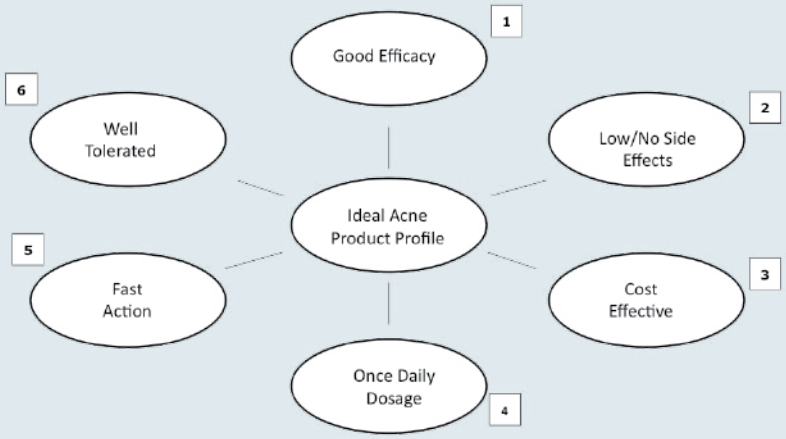
  "It is the most effective drugs and able to treat all types of acne problem. 70% to 80% of the patients do not have a relapse." – *Doctor quote*

  "The greatest advantage of oral isotretinoin is that the recurrent rate is much lower. It would be as low as 20% to 30% and is effective for most of the patients." – *Doctor quote*

- In an ideal world Dermatologists are looking for an acne treatment that offers good efficacy, low side effects, is cost effective, has a fast onset of action and is well tolerated.

  Currently no one product is felt to be ideal in efficacy and side effects, hence fuelling the use of combination therapy, but at the expense of cost and patient compliance/convenience.

Ideal Acne Product Profile – All Respondents



Acne Patient Severity

Patient Type	Total	Dermatologist	GP
% Mild	24	18	28
% Moderate	48	49	47
% Severe	28	33	25

Tipping Points for Presentation to a Physician

- **By far and away the main tipping point for presentation to a physician is previous treatment failure**
  - And in relation to the acne being uncontrolled for longer periods
- **The other lesser mentioned, but still important push factors**
  - Concern over image and appearance
  - Quality of life
- **A few smaller push factors were also given**
  - Friends/relatives urging to take the condition seriously
  - Social pressure
  - Recommendation by friends who have had acne treated
  - Aggravation of skin by facials/beauty salon

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