**Dr Mark Tang**

Dr Mark Tang is Senior Consultant Dermatologist and Director of Research, National Skin Centre (NSC), Singapore, as well as Clinical Teacher, School of Medicine, National University of Singapore (NUS). Dr Tang’s research interests include atopic dermatitis, acne genetics, antibiotic resistance in *P. acnes* and immunodermatology. Over the last 2 years, Dr Tang has been the principal investigator of a retrospective study on the use of isotretinoin in over 2500 patients with acne that showed high efficacy, good tolerability and overall safety with its use.

**Dr Marius Rademaker**

Dr Marius Rademaker is Clinical Director and Head of Department, Dermatology Department, Waikato District Health Board, and Honorary Associate Professor of Medicine, University of Auckland, New Zealand. Dr Rademaker graduated from Southampton University Medical School, UK in 1980, before progressing to attain numerous postgraduate qualifications and becoming fully accredited as a Dermatologist in 1989. He has served on various advisory committees for the Australian Medical Council and Medical Council of New Zealand. His clinical interests are paediatric dermatology, inflammatory dermatosis and contact dermatitis. In recent years he has been involved in a number of single and multicentre clinical trials of dermatological agents (itraconazole, Izalozole, 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.

### 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. 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. 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. 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 inflammatory response to *P. acnes*. In the short term, it is associated with significant social and psychological impacts in patients.

### 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. 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. Stress has been shown to aggravate acne. This is especially relevant in adolescents taking stressful exams, as seen in a Singapore study. 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. *P. acnes* resistance was seen more often in older patients and those with longer disease duration.

### Abbreviations used in this review

- CRH = corticotrophin-releasing hormone
- GI = glycemic 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

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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. 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. 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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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, 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.

**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.

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 epithelium 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 glycride fraction, and increases in cholesterol (relative), free sterols and total ceramides.

**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 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. 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). 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.

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

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

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. 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).

![Acne lesion score](image)

**Figure 4. Effects of isotretinoin 5 mg/day on number of acne lesions**

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.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Initial</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescent girls</td>
<td>10 mg/d for 2–3 mo</td>
<td>10 mg x 3×wk for 9–10 mo</td>
</tr>
<tr>
<td>Adolescent boys</td>
<td>10 mg/d for 4 mo</td>
<td>10 mg x 3×wk for 8 mo</td>
</tr>
<tr>
<td>Adults</td>
<td>10 mg/d for 3 mo or 5 mg/d*</td>
<td>10 mg x 3×wk for 1–2 yr or 5 mg/d* for 1–2 yr</td>
</tr>
</tbody>
</table>

*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

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 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.

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acne severity, young age, family history and truncal acne. 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 10 mg × 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 azathiaprine, 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.

**References**

• 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

1. Good Efficacy
2. Low/No Side Effects
3. Cost Effective
4. Once Daily Dosage
5. Fast Action
6. Well Tolerated

### Acne Patient Severity

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Total</th>
<th>Dermatologist</th>
<th>GP</th>
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<tbody>
<tr>
<td>% Mild</td>
<td>24</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>% Moderate</td>
<td>48</td>
<td>49</td>
<td>47</td>
</tr>
<tr>
<td>% Severe</td>
<td>28</td>
<td>33</td>
<td>25</td>
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</tbody>
</table>

### 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