

The 58th Annual Meeting of the American Academy of Dermatology

reported by Dr. W. M. Cheung and Dr. T. S. Au

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Organizer:	American Academy of Dermatology

Not All Cases of Onychomycosis are Created Equal: Reasons for Treatment Failure

Speaker: Dr. J. Q. Del Rosso

Several options exist for the treatment of fungal infections of the nails. Reported cure rates have improved over the years with the development of several newer topical agents, advanced delivery systems, the newer oral triazoles (itraconazole) and oral allylamines (terbinafine). Despite these improvements, there still exists a variability of response, with some patients exhibiting incomplete clearance or refractory disease. It then becomes necessary for physicians to develop innovative approaches utilizing adjustments to treatment or therapeutic combinations.

Because of the significant emphasis on comparative drug efficacy, morphologic and physical factors associated with onychomycosis are often forgotten as reasons for treatment failure, regardless of the drug prescribed. In this symposium, the speaker reviewed various physical factors that may reduce response to oral treatment for onychomycosis, especially when oral therapy is used alone.

Significant onycholysis

Extensive separation of the nail plate from the nail bed interferes with drug penetration into the underface of the nail plate. Debridement of the onycholytic nail plate eliminates this potential problem.

Lateral onychomycosis

Because of reduced contact area between the lateral

nail plate and the nail bed (compared to the central plate), drug penetration into the lateral plate may be reduced when lateral onychomycosis is present. This is most likely when lateral disease is thick and longitudinal. Mechanical removal of the lateral focus is recommended.

Spikes

Longitudinal bars or wedges of disease are sometimes noted in the nail plate and subungual region above the bed. Spikes appear to start distally and progress proximally, and have been associated with a lower response to oral drugs when used alone. Response rates to oral therapy are maximized when spikes are removed mechanically by debridement and wedge excision.

Dermatophytomas

Well-defined grey or yellow masses of disease in the nail plate and subungual region above the nail bed have been described. These are similar to spikes, except they are significantly wider in horizontal diameter. Histologically, these masses are hyperkeratotic, containing high concentrations of organism. Conceptually, they are "walled off" foci of disease that are most effectively treated when oral antifungal therapy is combined with mechanical removal.

Significant subungual debris/thickening

The presence of thick subungual involvement reduces the ability of drug to diffuse evenly through the affected nail bed and nail plate. The likelihood of sub-therapeutic concentrations of drug in portions of diseased nail is increased. Mechanical removal by debridement along with oral antifungal therapy may provide a better chance of disease eradication. Although formal studies are limited, the combination of oral antifungal therapy with mechanical therapy appears to be optimal when refractory patterns of clinical nail disease are identified.

Why Photodynamic Therapy?..... And for What?

Speaker: Dr. H. Lui

Photodynamic therapy (PDT) has been synonymous with the novel, somewhat experimental treatment of skin cancer using lasers and porphyrins. However, this is only partly true, since PDT can also involve non-laser light sources, and applied to an ever-expanding range of non-oncologic conditions. It shares similarities with PUVA therapy and laser surgery, but there are a number of important fundamental differences.

The typical clinical approach in PDT is to sequentially administer photosensitizers to the patient, either systemically or topically, and then expose the diseased tissue to light. The three essential ingredients for PDT are light, photosensitizing drug, and oxygen which is present in tissue.

Light photons are absorbed by the photosensitizing drug, which then becomes activated and enters a higher energy state. The activated drug in turn transfers its energy via a photochemical reaction to molecular oxygen within tissue to produce singlet oxygen which is highly reactive. This is a type II photochemical reaction. Singlet oxygen is not all that new or "exotic" to dermatology, since it is known that PUVA therapy can actually result in the production of singlet oxygen. The relative importance of singlet oxygen to the clinical effects of PUVA are unclear, but when one performs PUVA, one is also performing PDT in a technical sense. Singlet oxygen is highly reactive. It causes necrosis, induces apoptosis and possesses antimicrobial properties.

There are basic differences between photodynamic and photothermal uses of light. In the photodynamic reaction, the chromophore is administered as a drug (for example, amino-laevulinic acid). The absorbed light is converted to heat and lasers are not essential. However, in the photothermal reaction, the chromophore is present in tissue (for example, melanin). Chemical reactions are driven by the absorbed light. Pulsed lasers are ideal for this reaction.

The oncologic indications for PDT include basal

cell carcinoma, squamous cell carcinoma, actinic keratosis, cutaneous metastasis, mycosis fungoides, Kaposi's sarcoma, and tumor detection. The indications in non-oncologic conditions include psoriasis, hair removal, acne, alopecia areata, viral warts, vascular anomalies and skin resurfacing. However, with the exception of actinic keratosis, all of these indications are not currently approved by the Food and Drug Administration (FDA).

When treating psoriasis, PDT may be serving as an immunomodulator. Selective photosensitizers are taken up by activated lymphocytes. Lower PDT dose is required for treating psoriasis than for treating tumors, possibly because of different end results (apoptosis and necrosis respectively). Also, PDT drugs can accumulate in vascular tissues, and this may contribute to its clinical effects in psoriasis.

Drugs such as ALA may preferentially accumulate in the pilosebaceous apparatus, thereby providing a rationale for PDT in hair removal and acne.

Proposed mechanisms of action for skin cancer include direct tumor cell kill and ischaemic tumor necrosis via PDT effects on tumor vasculature. For nonmelanoma skin cancer, PDT may be most useful for patients with multiple superficial skin tumors such as nevoid basal cell carcinoma syndrome or patients with chronic arsenicism. For mycosis fungoides, there is some evidence that certain photosensitizers such as ALA preferentially accumulate in activated lymphocytes. Most PDT photosensitizers are fluorescent, providing a rationale for their use as an adjunct in tumor detection.

The advantages of PDT include simple concept, photosensitizer safety, treatment selectivity via drug delivery, and high patient acceptance. The disadvantages include dosimetry issues, two-step process, equipment, need for multiple treatments and lack of controlled studies at the moment.

With better understanding of PDT, it will certainly make an important part of our future dermatologic armamentarium.

Toxic Epidermal Necrolysis

Speaker: Dr. A. L. Licata

Many believe that toxic epidermal necrolysis (TEN) represents the severe end of a spectrum that also includes (in descending order of severity) Stevens-Johnson syndrome (SJS) and erythema multiforme (and some would add fixed drug reaction). The strongest evidence that these are related is a similarity in histopathology. However, clinically and etiologically there are marked differences. Many have tried to develop "criteria" to distinguish these entities, that is, number of mucous membranes involved or percent body surface area denuded, but to date none has been totally satisfactory. Recently, an international TEN study group evaluated 200 cases that most agreed were SJS or TEN with several interesting observations.

Firstly, there is no correlation between the extent or severity of mucosal erosions and the ultimate extent of epidermal detachment. Secondly, cases with "classic" targets (raised, well-defined, less than 3 cm, three distinct zones) never had widespread epidermal detachment. Thirdly, cases with primarily acral, classic targets tended to be related to infections and have a benign course; while cases with atypical lesions prominent on the face and torso tended to be drug related and have a higher morbidity. The most common drugs reported to be associated with TEN include anticonvulsants, allopurinol, NSAIDs, and sulfonamide antibiotics.

Treatment modalities include wound care, surveillance cultures, avoidance of prophylactic antibiotics, aggressive fluid and nutritional support. The role of systemic steroids was much debated. To date, there was no randomized prospective study regarding this issue. Multiple retrospective chart review studies concluded that systemic steroids increase morbidity and/or mortality and increase length of hospitalization.

In general, it is thought that recent improvements in survival have been due to advances in infection control and supportive care, allowing the patient to survive until re-epithelialization can occur.

Surgical Techniques in Children

Speaker: Annette M. Wagner

There are three important aspects to success in performing surgical procedures in children: (1) what procedures are necessary; (2) what the appropriate timing for the necessary procedure is; and (3) what type of anesthetic will be most successful.

What should come off?

The obvious indications that require removal are lesions that have premalignant potential or situation where a diagnostic or therapeutic biopsy is needed. Removal of atypical small congenital nevi, large congenital nevi, nevus sebaceous or atypical acquired nevi are appropriate. Removal of enlarging lesions such as pyogenic granuloma, pilomatricoma or dermoid cyst is also appropriate. The speaker also encouraged removing larger areas of aplasia cutis that are not covered by surrounding hair, or cosmetically important benign facial birthmarks in locations where removal would improve appearance.

Lesions that should be avoided include small, benign appearing congenital nevi or any acquired nevus on the face or anterior chest where the scar is usually less attractive than the nevus itself. Removal of self-resolving lesions such as juvenile xanthogranulomas, mastocytomas or hemangiomas should be avoided.

Time is everything

Many procedures in children can be safely postponed until the child is old enough to tolerate a local anesthetic. For example, excision of a small or medium sized congenital nevus or a small area of nevus sebaceous to prevent malignant change is best postponed till age 7-12. Late elementary school is preferable to middle school. Children are less active in sports and extra-curricular activities, and less concerned about appearance and have fewer 'adult' fears and preoccupation. Also, they usually obey post-operative instructions.

Excision of some lesions should not be postponed beyond age of eight. Giant congenital nevi present a risk of malignancy that is highest in the first several years of life. These should be dealt with as early as possible, usually beginning around three months of age. Tissue expansion of the scalp should be postponed until

six months to avoid molding of the skull. Round lesions that are larger than one centimeter or any shaped lesion larger than two centimeters on the scalp of an infant should be removed early because there is diminished scalp flexibility with time. What is a simple primary closure in a young baby rapidly becomes a multiple staged or tissue expansion closure on the scalp of an adolescent. Similarly, lesions on the acral extremities are often best approached in a younger child under general anesthesia.

Breast and genital lesions should be postponed until well into puberty to avoid distortion of the adult genitalia. Elective removal of lesions on the buttocks or groin should be postponed until the child is out of diapers to avoid increased risk of infection. Removal of vascular malformations of the lip should also be postponed for more than a year, when possible, to prevent unnecessary shortening of the lip due to excision in infancy.

What anesthetic is appropriate?

The majority of procedures in the pediatric population can be performed successfully in the outpatient clinic setting using a combination of topical, local and regional anesthesia. Regional blocks are underutilized in pediatric procedures. Digital blocks, ankle blocks and block of the lateral femoral cutaneous nerve are easily performed and less painful for children than infiltration with local anesthetic. The speaker frequently combined 0.23% bupivacaine with lidocaine (1:1) in the blocks to provide better post-operative anesthesia. Infiltration of the wound with local epinephrine, mostly for the hemostasis, is easily accomplished after a regional block. The speaker discouraged the use of conscious sedation of children in an office setting, unless someone skilled in pediatric resuscitation and the necessary equipment for monitoring and resuscitation are available. The most commonly used agents in pediatrics are a combination of fentanyl and midazolam or ketamine. Unfortunately, deaths had been reported with the use of these medications for minor procedures. Chloral hydrate and DPT (Demerol/Phenergan/Thorazine) are sedatives only. They do not provide sufficient analgesia for dermatologic procedures in children. For procedures done before age of seven, general anesthesia is more humane and appropriate.

Minimizing the pain of injection

Whenever possible, full advantage should be taken of the new topical anesthetic creams. EMLA effectively removes the pain of needle sticks. It does not, however, eliminate the burning with infiltration of the local anesthetic. If there is no time to wait for the effects of EMLA, using ice on the skin surface for 20-30 seconds or pinching the skin firmly before injection can also result in painless injection.

Other tricks can be used to minimize the pain of local injection. Buffering the xylocaine with sodium bicarbonate (9:1), and warming the local anesthetic to room temperature before injection will help. Never forget the power of distraction to minimize pain. Ask the children to blow away the pain like they blow out birthday candles.

Minimizing the trauma of surgery

The most important event in minimizing the trauma of pediatric skin surgery is the pre-operative counselling. It is critical that one explains simply but completely, exactly what one plans on doing and how one is going to do it. Stuffed animals or pillows of the child are invited. Parents are encouraged to stay with the children but one should beware of a fainting parent during the operation.

Surgical pearls:

- *Have an assistant if one is working on the scalp where bleeding is likely, or in an area where a closure under tension is expected.*
- *Count the stitches as one goes. Children always ask how many.*
- *Use a stronger suture than you think is necessary (for example 4/0 for scalp and back).*
- *While applying dressing, make it bulky for 48 hours to keep pressure on.*
- *Immobilize joints.*
- *If the wound is crusted, soak the wound first before suture is removed.*
- *Scars usually spread and are more pink in the first year; final colour and texture will be better.*

Use of Imiquimod in Non-Genital Lesions

reported by Dr. Y. P. Fung

Date:	28 February, 2000
Venue:	Yaumatei Skin Centre
Speaker:	Dr. Mark Seraly
Organizer:	HKSDV; Scientific Meeting

In this meeting, the speaker discussed the important immunological actions of imiquimod and outlined its clinical use in both genital and non-genital lesions.

Imiquimod is a nucleoside-analogue-like compound that has no anti-viral property of its own. It acts as an immuno-modulator by 1) stimulating cell-mediated TH1 response, 2) inducing cytokine production especially alpha interferon, interleukin-12 & tumor necrosis factor and 3) enhancing Langerhans cell activities, hence facilitates the production of memory cells.

Genital warts

In treating genital warts, conventional topical destructive chemotherapy and cryotherapy give recurrence rates between 30-40%. This figure is reduced to 13% with imiquimod because of its ability to enhance cell-mediated immunity. Clearance rate is superior in females (up to 50%) due to the natural occlusive effect of the female anatomy.

Common warts and flat warts

Topical application of imiquimod once or twice per day (5 days on and 2 days off) with or without occlusion has been shown to be effective in treating common warts and flat warts. Its efficacy is limited by penetration through the hyperkeratotic epidermal layer. Combination therapy with cryotherapy or topical salicylic acid followed by imiquimod application is currently under study. Application of imiquimod more than twice per day is not recommended. It has been shown that cytokine induction can be detected 2 hours after application. Its activity peaks at 8 hours and will remain for 24 hours. Application of imiquimod more

than twice per day may result in downregulation of immune response. Periungual warts and common warts respond well to topical imiquimod, but plantar warts show less favorable response, probably due to difficult penetration.

Intra-vaginal and cervical warts

One third of women with external genital warts have intra-vaginal and cervical warts. 10% of patient with genital warts caused by human papillomavirus 16 and 18 will develop cervical intraepithelial neoplasia (CIN). The treatment of intravaginal and cervical warts with imiquimod and its impact on CIN is currently under study.

Molluscum contagiosum

Molluscum contagiosum shows good response to imiquimod. In a study of 100 male patients (age 9-27) followed up for one year, 1% imiquimod applied three times per day for four 5-day-week cycles cleared 86.3% of the lesions and gave a cure rate of 82%. Pilot study using topical 5% imiquimod in children for assessing its safety showed no significant undesirable local and systemic effects. Imiquimod plays a useful role in treating patients with multiple molluscum contagiosum at different body areas when other simple operative procedures become undesirable. When using imiquimod for molluscum contagiosum and plane warts, most patients respond in 6-8 weeks when applying once per day, in a 5-day-week.

Herpes simplex virus (HSV)

It is found in animal studies that if imiquimod was applied within 24 to 48 hours of HSV inoculation, the animal was protected from infection. This finding may have important implications for prophylaxis of HSV. Pilot study had shown good response when used in patient with prodromal symptomatic HSV.

Imiquimod as an anti-tumor agent

Imiquimod has been shown to have anti-tumor

effects in basal cell carcinoma, Bowen's disease, Bowenoid papulosis, actinic keratosis, cutaneous T cell lymphoma, Kaposi sarcoma, melanoma and neonatal capillary haemangioma.

For basal cell carcinoma, it takes 8-12 weeks to work. Its use should be considered in the following settings: elderly, debilitated nursing home candidate, non-surgical candidate, patients on anti-coagulant, patients with infectious disease, patients with basal cell carcinoma syndromes and those who refuse surgery. Its use is also being considered for prophylaxis after surgical excision of the primary tumor.

Imiquimod plays an important role if the lesion is located at anatomically difficult sites like Bowen's disease at glan penis. It avoids unpleasant surgery, scarring and hyperpigmentation. Patients may fail to respond to imiquimod if the lesion is complicated by secondary bacterial infection. This may be secondary to the diminished TH2 humoral response as a result of the enhanced TH1 activity by imiquimod.

Problems of imiquimod in treating tumors

Imiquimod is inappropriate for treating head and neck tumors, high-risk tumors and recurrent skin cancer. Its long treatment period and absence of histological control also limit its use.

Other uses

Conditions that may respond to topical imiquimod include vitiligo, alopecia areata and others that may regress with a diminished TH2 response. Hepatitis B and C, multiple sclerosis, renal cell carcinoma, chronic myeloid leukemia and carcinoid tumor may respond to oral imiquimod but it is known to cause significant nausea.

For treatment in patients with AIDS, when imiquimod was first developed, its effect in these patients is no different from placebo. These were used in patients without CD4 monitoring and before the days of protease inhibitors. With the common use of protease inhibitor and CD4 monitoring nowadays, AIDS patients with higher CD4 count respond well to imiquimod.

Learning points:

In USA, as imiquimod has not yet been approved by the FDA for uses other than the treatment of external genital and peri-anal warts, patient's consent must be obtained before prescribing the agent for other purposes.

Skin Diseases First Described in Japan

reported by Dr. W. S. Lam

Date:	29 March, 2000
Venue:	8/F, Sai Ying Pun Jockey Club Clinic
Speaker:	Prof. Takeji Nishkawa
Organizer:	Social Hygiene Service, DH; Scientific Meeting

The speaker discussed on several skin diseases that were first described by Japanese dermatologists. The specialty of dermatology in Japan could be dated back to 1901 when the Japanese Dermatological Association Incorporated was established by Keizo Dohi.

Eosinophilic pustular folliculitis

It was first described by Ofuji in 1970. It occurs predominantly in male, presenting as recurrent, follicular, eruptive papulopustules. Groups of papulopustules spread peripherally with central clearing, forming annular lesions or plaques. Face and trunk are frequently involved. About 20% of patients have palmoplantar involvement, simulating palmoplantar pustulosis. Intermittent exacerbations are associated with circulating leucocytosis and eosinophilia. Pathological examination shows inflammatory infiltrate surrounding the hair follicles with tissue eosinophilia.

Differential diagnoses include tinea corporis, acne vulgaris, pustular psoriasis, eczema and HIV-associated folliculitis. For HIV-associated folliculitis, the lesions appear as itchy discrete erythematous follicular papules associated with normal or decreased circulating leucocyte count. This is in contrast to eosinophilic pustular folliculitis which is itchy in less than 50% of patients and appears as coalescing papulopustular plaques associated with leucocytosis.

Factors involved in pathogenesis include high sebaceous activity, hypersensitivity to metal or other exogenous antigen, type 1 allergy to epidermal component and eosinophil chemotactic factors.

According to the experience of the Japanese

dermatologists, indomethacin is often effective and is the preferred drug of choice.

Prurigo pigmentosa

It was first described by Nagashima in 1971. It predominantly occurs in young female. The disease presents as recurrent itchy erythematous papules which coalesce to form a reticular pattern on breast and back, resulting as reticular pigmentation later. Pathological examination shows lichenoid tissue reaction.

Differential diagnoses include lichen planus, pigmented contact dermatitis, dermatitis herpetiformis and reticular erythematous mucinosis syndrome. Postulated pathogenetic factors include contact allergy to clothes, follicular changes secondary to pityrosporum and ketosis due to fasting or dieting.

Minocycline and dapsone are effective. Some patients do cure spontaneously in the long run. The disease is regarded as an established entity in Japan but it is not quite recognized outside Japan.

Annular erythema due to Sjogren's syndrome

Annular erythema was reported by Japanese dermatologists in patients with Sjogren's syndrome.

It presents as recurrent, annular erythematous rash with raised edematous border and central clearing on face, upper extremities and back. Scale and post-inflammatory pigmentation is either absent or minimal. This is in contrast to subacute cutaneous lupus erythematosus (SCLE) which is an annular and/or polycyclic rash with more prominent scaling and post-inflammatory pigmentation. Histologically the former shows no significant change in the epidermis and patchy lymphocytic infiltration in the dermis. On the other hand, the latter shows features compatible with lupus erythematosus in the epidermis and lymphocytic infiltration in the upper dermis.

Differential diagnoses include SCLE, Sweet's

syndrome, erythema multiforme (EM), erythema annulare centrifugum, Rowell's syndrome (lupus erythematosus associated with EM-like lesions).

The significance of the rash is that its presence would prompt investigations for Sjogren's syndrome like anti-Ro antibody, anti-La antibody, tests for sicca syndrome and lip biopsy.

Treatment includes low-dose prednisolone (10-20 mg/day), dapsone and non-steroidal anti-inflammatory drugs.

Conclusion

The speaker hoped that, with increasing recognition of the above three skin diseases first described in Japan, more cases could be reported in other Asian countries.

Learning points:

Eosinophilic pustular folliculitis in immunocompetent patients reported in Japan and HIV-associated folliculitis more recognized in the Western world have distinct clinical difference. Ethnic dermatology is an emerging specialty.

The Research and Development Process of New Drugs

reported by Dr. W. S. Lam

Date:	8 March, 2000
Venue:	Yaumatei Skin Centre
Speaker:	Dr. G. S. N. Lau
Organizer:	Social Hygiene Service, DH; Clinico-pathological Seminar

It takes about 12 years on average for an experimental drug to travel from laboratory to medicine chest. Statistically, only 5 in 4,000 compounds screened in preclinical testing are eventually approved for human testing.

There are 5 phases for drug development: preclinical testing, phase I, phase II, phase III and phase IV.

Preclinical testing

Preclinical testing involves discovery and testing of new chemical entities (NCEs). A new chemical entity can be discovered by serendipity, predicted chemical structure synthesis, targeted mechanistic-specific molecule design or massive screening for potential action. Preclinical testing includes assessment of biological activity, safety, toxicity and carcinogenicity. These are done through laboratory-based tests (like cell culture) and animal tests. The process takes more than

three years and, if successful, is concluded by the granting of a license to enter phase I testing, for example, investigational new drug (IND) status in the United States.

Phase I

It involves the initial administration of an investigational new drug (IND) into human volunteers, that is, human pharmacology study. It includes assessment of initial human safety and tolerability, pharmacokinetics, pharmacodynamics and early measurement of drug activity. The process takes about one year.

Phase II

It explores the therapeutic efficacy of an IND in patients. Their therapeutic effects are compared to controls or established agents. These patients are selected by narrow criteria. It includes dose determination as well as evaluation of potential study endpoints, therapeutic regimens (for example, concomitant medications) and target populations. The process takes about two years.

Phase III

It serves to demonstrate or confirm therapeutic

benefit. It includes pivotal studies for regulatory purpose and provides adequate basis for marketing approval in terms of safety and efficacy. These studies involve a larger and wider population (thousands of subjects) in different stages of disease, and often on other medications, over an extended period. The whole process takes about three years.

Phase IV

Phase IV begins after drug approval and refers to post-marketing surveillance. It includes safety monitoring, additional studies on therapeutic use, drug-drug or drug-food interaction, safety studies, etc.

A summary of the whole drug development and approval process is given in Table 1. In Hong Kong, the approval process is completed by obtaining the 'Registration Certificate' from the Department of Health. Some countries require local data for drug registration because of possible ethnic difference. Attempt to unify the requirement for drug registration has been made by the International Conference on Harmonization (web site: <http://www.ifpma.org.ich1.html>).

Other studies for special considerations

Other studies may be carried out after drug approval. These include research on drug metabolites, use in pregnant or nursing women, use in paediatric population, orphan indications, outcomes studies, pharmaco-economic studies, etc. Outcomes studies measure patient-related outcomes and are important for evidence-based medicine. It involves a large number of patients over a long period. Pharmaco-economic studies assess the use of a medication in economic terms through analysis of outcome data and clinical trials. A comparison of clinical, outcomes and pharmaco-economic research is given in Table 2. Data from the latter two kinds of research is increasingly required by health care providers to determine the need of certain new drugs. The expense of running these studies will add to the cost of new medications.

Cost considerations for drug development

For new drug application (NDA) at the Food and Drug Administration in the United States, the number of clinical trials has doubled and number of patients per trial has tripled since 1970's. One NDA has more

Table 1. Drug development and approval process

Stage	Preclinical testing		Phase I	Phase II	Phase III		Approval process	
Years	3.5		1	2	3		2.5	Total = 12 years
Test population	Laboratory and animal studies	FILE	20-80 healthy volunteers	100-300 patient volunteers		FILE		
Purpose	Assess safety and biological activity	IND*	Determine safety and dosage	Evaluate effectiveness. Look for side effects.	Verify effectiveness, monitor adverse reactions from long-term use.	NDA#	Review process	<i>Post-marketing Surveillance (Phase IV)</i>
				Expedited review: Phases II and III combined to shorten approval process on new medicines for serious and life-threatening diseases.				
% of all new drug that pass	0.125% of all new chemical entities tested		70% of INDs*	33% of INDs*	27% of INDs*		20% of INDs*	

*IND - Investigational New Drug

#NDA - New drug application (at Food and Drug Administration, United States)

Table 2. Comparison of clinical, outcomes and pharmaco-economic research

	Clinical research	Outcomes research	Pharmaco-economic research
Main aim	To determine efficacy	To determine effectiveness	To determine efficiency
Study design	Randomised clinical trials	Observational studies and randomised clinical trials	Economic analyses based on outcomes data and clinical trials
Main measures	-Efficacy and safety -Intermediate endpoints	-Patient-related outcomes	-Costs and outcomes
Time-frame	Short term	Long term	Long term
Based on	Ideal (not normal) clinical practice	Normal clinical practice	Normal clinical practice

than 100,000 pages. For one successful drug, the total cost for the whole process from preclinical testing to approval is about US\$500 million.

Evaluation of generic drugs

The patent right for a new drug is 20 years, starting from the preclinical stage. Application for a patent is therefore made as soon as possible, usually in the preclinical testing stage. During this 20-year period, the owner of the patent has exclusive right to make the drug. On expiry of the patent, other companies can produce the generic form of the original drug. For registration of a generic drug, it is necessary to demonstrate bioequivalence of the product is comparable to the original drug.

Conclusion

Drug development and approval is a time-consuming and costly process. In addition to the need to demonstrate safety and efficacy of a new drug, increasing emphasis is placed on its effectiveness and efficiency in the health care system.

Learning points:

In order to earn a place in the therapeutic regimen, a new drug needs to meet requirements in safety and efficacy evaluation as well as effectiveness and efficiency assessment.