The Korean Society for Psoriasis

Seoul Psoriasis Symposium for Biologics & Systemic Agents

Mar 23 (Sat), 2013

Samsung Medical Center, Cancer Center Building, B1 Auditorium, Seoul, Korea

삼성서울병원 암센터 지하 1층 강당

Organized by
The Korean Society for Psoriasis
Sponsored by
The Korean Dermatological Association

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PROGRAM

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인사말씀

안녕하십니까?

2013년 새봄을 알리는 이 계절에 건선치료에 사용되는 생물학적제제와 전통적 경구치료제제에 대한 심포지움을 개최하게 됨을 기쁘게 생각합니다. 대한건선학회는 2012년 부산에서 건선에 사용되는 생물학적제제에 대한 심포지움을 개최한 바 있습니다. 그간 학술대회라는 형식을 빌어 생물학적제제에 대한 이론적 강의를 한 적은 많이 있었으나 본격적인 CME를 시작한 것은 거의 처음이었으며 더구나 지방을 찾아 이를 시작하였다는 것은 신선한 충격으로 받아들여지면서 피부과 회원들의 많은 호응이 있었습니다.

금년에는 이에 힘입어 2회에 걸쳐 CME를 하기로 하고 그 첫 회를 서울에서 개최합니다. 또한 기존의 생물학적제제 심포지움을 확대하여 생물학적제제 사용의 관문이 되는 전통적 전신요법에 대한 강의도 추가하였습니다. 최근 건선 치료는 보다 빠른 속도로 치료 강도를 증가시키고 또한 국소치료제의 영역인 경증 건선의 범위도 축소시키는 경향을 보이고 있어서 생물학적제제를 포함한 전신치료제의 사용 빈도는 급속히 증가하고 있습니다. 그러나 아직도 많은 피부과 의사들이 건선치료에 있어서 국소치료제 외에는 다소 부담스럽게 생각하는 경향을 보이고 있으며 이는 수련과정 혹은 전문의 취득 이후에 전신 치료제 사용에 대한 실질적인 교육기회와 경험이 부족하였던 것과 무관하지 않다고 생각합니다.

점점 피부과 이외의 다른 전공분야에서까지 건선환자의 진료에 관심을 기울이는 경향을 심각히 우려하며 대한건선학회는 회원여러분들이 보다 차별화된 치료역량을 강화할 수 있도록 노력하고자 합니다. 이번 심포지움은 건선치료에 있어서 매우 실질적인 측면들을 다루게 되며 특히 독일 J.W. Goethe University의 Diamant Thaçi 교수의 건선의 치료 표적에 대한 특강과 일본 Tokai University의 Mabuchi 교수로 부터 최근 일본에서의 생물학적제제 사용경험에 관한 발표도 준비되어 있습니다.

아무쪼록 이번 심포지움에 많이 참석하시어 건선치료 역량 강화에 있어 좋은 결과 있으시길 바랍니다. 끝으로 이번 심포지움 준비를 위해 고생한 대한건선학회 임원 여러분의 노고에 감사드립니다.

2013. 3. 23

대한건선학회 회장 **이 주 홍**

PROGRAM

Opening Ceremony

12:30-1:00 Registration

12:50-1:00 Opening address: Joo-Heung LEE (*President of KSP*)
Congratulatory address: Young-Chul KYE (*Chairman of KDA*)

1:00-2:30 Session 1 Conventional Systemic Agents

Chairs: Kwang Joong KIM (*Hallym University*), Young-Chul KYE (*Korea University*)

Q&A (10 min)

2:30-3:40 Session 2 Biologic Agents

Chairs: Nack-In KIM (*Kyung Hee University*), Akira OZAWA (*Tokai University, Japan*)

Q&A (10 min)

3:40-3:55 *Coffee break*

3:55-4:40 **Session 3 Special Lecture**
Chair: Jai Il YOUN (*National Medical Center*)

S3-1. **Future targets and new drugs for psoriatic disease -small molecules and biologics-** **/ 27**
Diamant THAÇI (*J.W. Goethe University, Germany*)

4:40-5:50 **Session 4 Field experiences with biologics**
Chairs: Young-Suck RO (*Hanyang University*), Shigaku IKEDA (*Juntendo University, Japan*)

S4-1. **Field experiences with Enbrel®** **/ 43**
Jee-Ho CHOI (*Ulsan University*)
S4-2. **Field experiences with Stelara®** **/ 44**
Sang-Woong YOUN (*Seoul National University*)
S4-3. **Field experiences with Humira® [Invited Lecture]** **/ 45**
Tomotaka MABUCHI (*Tokai University, Japan*)
S4-4. **Reimbursement strategy** **/ 46**
Jae-We CHO (*Keimyung University*)

Q&A (10 min)

Closing

Session 1

Conventional Systemic Agents

S1-1

Changing paradigm of psoriasis treatment

Joo-Heung LEE

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Psoriasis treatment paradigm has changed gradually but obviously over the past decades. Core concept of the new paradigm can be summarized as 'higher potency' 'rapid escalation' and 'continuity' of treatment. The advent of the new paradigm was prompted partly because of dramatic impact that biologics have made in the treatment of psoriasis. But main drive of the change came from the strong voices of the patients themselves.

In contrast to several decades ago, fast-acting, potent and relatively safe oral medication such as cyclosporine or methotrexate is now widely used, although long-term treatment with them is not recommended because of major organ toxicities. Innovation in the field of phototherapy for more effective, targeted and even safer devices has also contributed to the emergence of new paradigm. Furthermore, traditional concept of mild to moderate psoriasis has changed. Some even suggests mild psoriasis should be defined as psoriasis involving less than 2% of the total body surface area, much smaller area for mild psoriasis than was suggested a few decades ago. These trends jeopardized the positioning and value of topical treatments that used to be the mainstay for the mild to moderate psoriasis. However, the new trend has not only affected topical treatments. It also undermined the area of conventional systemic agents. While the conventional systemic agents can only offer on-and-off treatment, biologics can allegedly provide long-term or even life-long treatment like other long-term medications in chronic disorders such as diabetes.

Patients' voices are the major driver for more potent, rapid escalating and long-lasting treatment. Recent surveys carried out in Europe and US showed that treatment satisfaction level of psoriasis patients is surprisingly low in contrast to the expectation of dermatologists. Major reasons for the dissatisfaction are time consuming nature and lack of efficacy that are mostly attributed to topical treatments. Many psoriasis patients do not want to waste time and effort in doing apparently ineffective topical treatments. Patients' voices that used to be a 'storm in a teacup' is now spilling over and steering a new paradigm. Their perspective is now being reflected in the treatment guidelines in the form of QoL-based severity measures. S3 European guideline is a great example by incorporating DLQI in the treatment guideline.

In conclusion, we, dermatologists, are being invited to the new world of psoriasis treatment and if we really want to keep our leading role in the management of psoriasis, we should not only be well prepared but also be proactive for the new paradigm.

S1-2

Cyclosporine in psoriasis treatment

Jee-Ho CHOI

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1. Mechanism of action and indications

Cyclosporine forms a complex with cyclophilin, which inactives calcineurin phosphorylase, preventing the phosphorylation of nuclear factor of activated T cells and, therefore, the transcription of IL-2. Cyclosporine is one of the most effective treatments for psoriasis because of its rapid onset of action. In patients with severe psoriasis unresponsive to other treatments, cyclosporine can induce a rapid remission, and can be used as a bridge to other therapies. As with most therapeutic agents in psoriasis, there is limited data regarding the efficacy of cyclosporine in other forms of psoriasis such as chronic palmoplantar pustulosis (PPP), generalized pustular psoriasis (GPP), nail psoriasis, guttate psoriasis and erythrodermic psoriasis. Cyclosporine is contraindicated in uncontrolled hypertension, renal disease, serious infections, and in those with a previous history of malignancy, excluding basal cell carcinoma.

2. Efficacy

Efficacy of cyclosporine is dose dependent with a shorter time to remission at higher doses. Cyclosporine at doses of 2.5 to 5 mg/kg/d for a 12- to 16-week period produces rapid and significant improvement in psoriasis in 80% to 90% of patients. At 3 mg/kg/d, PASI 75 is achieved in 50% to 70% of patients and PASI 90 in 30% to 50% of patients. Cyclosporine is also effective in treating pustular, erythrodermic, and nail psoriasis.

3. Dosage

An initial low-dose approach (starting at 2.5 mg/kg/d) is appropriate for patients with stable psoriasis, whose severity is between moderate and severe. An initial high-dose approach (5.0 mg/kg/d) is appropriate for patients with severe psoriasis, patients with psoriasis recalcitrant to other treatments, or for those patients who are highly distressed in a crisis situation. Once a patient's psoriasis is in remission, the goal is to maintain the patient on the minimum effective dose. Intermittent short-term therapy (12~16 weeks) is the most frequently recommended regimen, using short courses of cyclosporine until significant improvement is achieved, after which treatment is withdrawn. A short course of cyclosporine can be used in severe flares of disease as rescue therapy because of its rapid onset of action until an alternative maintenance treatment is instituted. This is particularly useful in the treatment of erythrodermic, or generalized pustular psoriasis.

4. Combination therapy

Cyclosporine can be combined with topical therapies, such as corticosteroids or vitamin D3 analogues for an improved response. Systemic treatments, such as methotrexate, acitretin, can also be used in combination with cyclosporine in severe cases, allowing for dose reduction of cyclosporine to minimize toxicity. Rotational therapy with the aforementioned systemic agents can also be used to minimize duration of cyclosporine treatment and toxicity.

5. Safety and monitoring

If serum creatinine increases 30% over the patient's baseline value on two consecutive readings 2 weeks apart, the dose should be reduced. If there is an elevation of serum creatinine of at least 30% over the patient's baseline value, recorded on two consecutive readings 2 weeks apart, the dose should be reduced by 1 mg/kg/day or by 25% to 50% for a minimum of 4 weeks, even if the value lies within the normal reference range. If serum creatinine does not improve after 4 weeks therapy at the reduced dose, cyclosporine should be decreased by another 25% to 50%. If creatinine remains elevated at this stage, cyclosporine should be discontinued. A maximum dose of 5 mg/kg should be used for up to 2 year only. Patients treated continuously for more than 2 years have a significantly higher risk of developing irreversible renal damage. In one study, elevations of creatinine greater than 30% of baseline were found in 71% of patients who had been treated with CSA for an average of 4.5 years. In the majority of these patients, creatinine levels stabilized but did not return to baseline levels after the CSA dosage was decreased. Renal structural changes including slight to moderate interstitial fibrosis were observed in psoriatic patients treated with cyclosporine for 1-2 years, significant lesions such as glomerular sclerosis or severe interstitial fibrosis being observed after 3 years or more. When hypertension develops, the dose should be reduced by 25% to 50% or antihypertensive therapy introduced. Calcium channel blockers of the dihydropyridine class are the antihypertensives of choice. Experimental studies have shown that cyclosporine is not genotoxic but causes dose- dependent tumor promotion. In skin tumor models, cyclosporine has been shown to enhance the induction of skin tumors by ultraviolet irradiation. Because cyclosporine has been reported to cause the reactivation of latent tuberculosis infection in higher doses used in transplant recipients, and because cyclosporine is an immunosuppressant, the National Psoriasis Foundation recommends screening for latent tuberculosis infection before initiation of cyclosporine treatment.

6. Drug interactions

Because cyclosporine is metabolized by the cytochrome P450 3A4 system, there are important drug interactions that will alter cyclosporine levels. Macrolides, azole antifungals, and calcium channel blockers increase cyclosporine levels. Anticonvulsants, rifampin, and griseofulvin decrease cyclosporine levels. It is also important to note that foods that contain grapefruit juice can increase levels of cyclosporine in the serum. Cyclosporine crosses the placental blood barrier and is a category C drug in pregnancy.

S1-3

Methotrexate in psoriasis treatment

Chul Jong PARK

Department of Dermatology, Pusan National University School of Medicine, Korea

Methotrexate was first used for the treatment of psoriasis over 50 years ago. High-quality data concerning its efficacy and side effects are sparse. Monotherapy and combination therapy with methotrexate continue to be widely used in dermatology primarily in psoriasis and psoriatic arthritis, and for diseases as varied as sarcoidosis, dermatomyositis, and pyoderma gangrenosum.

Methotrexate is a safe and effective drug for the treatment of psoriasis. Appropriate patient selection and monitoring will significantly decrease the risks of side effects. In patients without risk factors for hepatic fibrosis, liver biopsies may not be indicated or the frequency of liver biopsies may be markedly reduced.

Table I. Monitoring for hapatotoxicity in low-risk patients

No baseline liver biopsy
Monitor liver function tests monthly for the first 6 months and then every 1 to 2 months thereafter.
→ For minor elevations (<2-fold upper limit of normal), repeat in 2 to 4 weeks.
→ For moderate elevations (>2-fold but <3-fold upper limit of normal), closely monitor, repeat in 2 to 4 weeks, and dose reductions as necessary.
→ For persistent elevations in 5 of 9 AST levels over a 12-month period or if there is a decline in serum albumin with normal nutritional status below the normal range in the setting of well-controlled disease, liver biopsy should be performed.
Consider continuing to follow according to above ACR guidelines without biopsy
Or
Consider liver biopsy after 3.5 to 4.0 g total cumulative dosage
Or
Consider switching to another agent or discontinuing therapy after 3.5 to 4.0 g total cumulative dosage.

ACR, American College of Rheumatology; *AST*, serum aspartate aminotransferase.

Table II. Monitoring for hepatotoxicity in high-risk patients

Consider the use of a different systemic agent.
Consider delayed baseline liver biopsy (after 2 to 6 months of therapy to establish medication efficacy and tolerability).
Repeat liver biopsies after approximately 1.0 to 1.5 g of therapy.

Decades after its introduction, methotrexate remains an effective treatment in the therapeutic armamentarium of dermatologists. Despite the introduction of biologics, methotrexate is regularly used alone or in combination with biologics for the treatment of psoriasis, and it remains a valuable treatment option in many other dermatologic diseases. Safe and effective use of methotrexate requires rational patient selection and, subsequently, fastidious and appropriate monitoring. Importantly, the clinician must recognize that patients differ in their inherent risks while taking methotrexate, with issues such as comorbidities and concomitant drug use always in need of consideration. Awareness of the risk factors for hematologic toxicity, primarily decreased renal function, will significantly reduce this side effect. Awareness of the risks for hepatic toxicity is also crucial. Patients without hepatic risk factors may not require routine liver biopsies. Folic acid supplementation is recommended to increase the safety and decrease the potential side effects.

References

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S1-4

Acitretin in psoriasis treatment

Bong-Seok SHIN

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Acitretin, a synthetic second generation retinoid, is the pharmacologically active metabolite of etretinate, and is the only oral retinoid currently approved by the FDA for treatment of severe psoriasis. Acitretin has replaced etretinate in the late 1980s in most countries because of its more favorable pharmacokinetic profile. Bioavailability is enhanced by food, especially fatty food. Acitretin is 50 times less lipophilic than etretinate and binds to albumin, whereas etretinate binds strongly to plasma lipoprotein. Etretinate is stored in adipose tissue from which it is released slowly, so it has a terminal half-life of up to 120 days in contrast to only 2 days in acitretin. But small amounts of etretinate can be formed in patients receiving acitretin if it is taken simultaneously with alcohol. Therefore the time of compulsory contraception in patients receiving acitretin is extended to 2 years (3years in the US)

Acitretin reduces the proliferative activity and favors the differentiation of epidermal keratinocytes. It inhibits keratinocyte production of VEGF, and reduces intraepidermal migration of neutrophils. Also it inhibits IL-6-driven induction of Th17 cells and promotes the differentiation of T-regulatory cells.

Acitretin monotherapy is recommended in the treatment of psoriasis, hyperkeratotic hand eczema, severe Darier disease, severe congenital ichthyosis, keratoderma, lichen planus, lichen sclerosus, discoid LE, and premalignant and malignant skin lesions.

Starting daily dosages between 10 and 25 mg and stepwise escalation are generally associated with higher clinical efficacy and lower incidence of adverse events and are safe in both the short-term and long-term treatments of psoriasis.

Acitretin as single agent therapy appear to show limited efficacy in psoriasis vulgaris (PV). Acitretin appears to provide better efficacy in pustular psoriasis (palmoplantar and generalized von Zumbusch type) than in PV as a single agent treatment. Therefore, combining retinoids with phototherapy appear to be highly effective in patients with PV. These combinations show an increased efficacy compared to monotherapy with acitretin or UVB or PUVA. An additional advantage is that lower doses of acitretin and lower cumulative doses of UV. Also, the possible combination with acitretin is topical agents, but methotrexate with increased hepatotoxicity and cyclosporin with no evidence of increased efficacy are not recommended.

Clinically significant drug interaction may occur with methotrexate, tetracycline, mini-pill,

phenytoin, antidiabetic agents, and corticosteroids that should be avoided or used with caution.

Side effects (teratogenicity, mucocutaneous effects, hepatotoxicity, hyperlipidemia, and skeletal abnormalities) are seen in most patients receiving acitretin. But they usually disappear when the drug is reduced or withdrawn, except for hyperostosis. There is no strong evidence of an increased risk of skeletal abnormalities in psoriasis patients treated with retinoids in recent many published studies.

Acitretin therapy should be monitored with liver enzymes, fasting serum cholesterol and TG, blood sugar level, and radiological investigation and this is the responsibility of the supervising dermatologist.

Recently, acitretin has revisited in the era of biologics. Compared with other systemic therapies, acitretin hardly affects the immune system, which explains the unique position of acitretin. This could be an argument to choose acitretin over the other systemic therapies in specific patient populations (immunocompromised patients, patients prone to infection, patients with a history of high cumulative doses of UV or other patients with an increased risk of skin malignancies, HIV-positive patients with psoriasis, and patients living in areas with endemic occurrence of infections such as tuberculosis).

And, acitretin could be an interesting candidate for combination treatment with biologics, since there will be no additional suppression of the immune system and that means there could well be a synergistic effect without increasing the risk of toxicity. Case reports of successful combination of acitretin with infliximab or adalimumab or efalizumab or etanercept have reported in refractory psoriasis recently.

Session 2

Biologic Agents

S2-1

Biologics: when to start? When to stop? And what to choose?

Yong-Beom CHOE

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The advent of biological therapy has revolutionized psoriasis care. Nonetheless, not all patients require biological therapy. Selection of patients depends on clinical characteristics, previous response to other medical therapy, and comorbid conditions. Availability, reimbursement guidelines, and patient preferences guide the choice of therapy for psoriasis. Currently, the biologics approved by the Korean Food and Drug Administration (KFDA) are divided into 2 classes: tumor necrosis factor (TNF)-α inhibitors, and interleukin (IL)-12/23 inhibitors. TNF-α inhibitors (etanercept, infliximab, adalimumab) has the most extensive clinical trial data, but newly developed ustekinumab appear to have similar or better benefits in plaque psoriasis. Moderate to severe psoriasis (PASI>10, BSA>10) not responding to conventional systemic agents for more than 3 months is an indication for starting biological therapy. Patients who respond to therapy (PASI75 response) at 12~16 weeks could get another 6 month treatment. After this point, every six month reevaluation of confirming drug efficacy prolong the use of biologics. Multiple factors will determine which of the four available biologics should be used first in a particular patient. This includes those related to the drug itself and how they relate to the clinical circumstance, patient preferences (e.g. mode of administration) and access, the latter being determined largely by health insurance guideline and patient`s economic status. In the short term, the monoclonal antibodies (infliximab, adalimumab, ustekinumab) seem to have a quicker onset of action, and are more effective than etanercept, although by 1 year the proportion of patients maintaining a PASI 75 may be comparable. With respect to safety, systematic review of data from short-term studies suggests that the risk of adverse events may be slightly higher with infliximab compared with etanercept and adalimumab while registry data indicate that risks of reactivation of tuberculosis and herpes zoster may be greater with adalimumab and infliximab as compared with etanercept. Ustekinumab is more effective than etanercept in the short term and is probably of comparable efficacy to adalimumab and infliximab, but safety data are very limited. Ustekinumab might therefore be reserved for patients who have failed or cannot use TNF-α antagonists. Patients who have a diminished or loss of response to one biologic agent may respond to switching to another agent. There are only limited efficacy data on use of a second biologic therapy in patients with psoriasis where the first has failed. Mechanisms underlying

primary failure (inadequate response following initiation of treatment) or secondary failure (loss of response over time) are poorly understood, although in the case of TNF-α antagonists, development of antidrug antibodies with consequent reduction in circulating drug levels is well described with both infliximab and adalimumab. Further, while infliximab, adalimumab and etanercept all act to block TNF-α, they are pharmacologically distinct. Thus failure to respond to one TNF-α antagonist may not preclude response to a second. This is supported by findings in a small open-label study and retrospective case cohort review which demonstrate efficacy of adalimumab following etanercept failure. Of note, approximately a third of patients entered into ustekinumab RCTs had been previously treated with biologic therapy (predominantly TNF-α antagonists), and this did not influence therapeutic outcome. Careful consideration should be given to the reasons for loss of response when switching to another biologic. There are insufficient data to make recommendations on when to stop biologic therapy. Therapy should be discontinued when patients fail to achieve an adequate response following treatment initiation or when treatment response is not maintained. Withdrawal of therapy is also indicated due to the following events: (i) a serious adverse event. Serious adverse events which may justify the withdrawal of treatment include malignancy, severe drug-related toxicity, severe infection (ii) pregnancy (iii) elective surgical procedures. A possible complication of an abruptly discontinued therapy is a flare of psoriasis. In this scenario, cyclosporine or methotrexate may be used for a few months to suppress disease and same or another biologic may be used subsequently.

S2-2

Making sure biologics are safe: Recent update

Byung-Soo KIM

Department of Dermatology, Pusan National University School of Medicine, Korea

Biologic agents targeting specific immune mediators have emerged as an alternative treatment option for patients with moderate-to-severe plaque psoriasis who are unresponsive to, or intolerant of, non-biologic systemic agents. Because they are processed by the same pathways as naturally occurring proteins in the human body, available data generally assert that approved biologic therapies can be considered safe and well tolerated in the short-term and also for longer periods. However, treatment guidelines still recommend them as second- or third-line therapies due to a relative lack of long-term safety data.

Due to their immunosuppressive activity, some anti-TNFs have been associated with a small increased risk of infection in patients with psoriasis and psoriatic arthritis, and studies of TNF antagonist use in other disease areas have raised concerns over a potential link to cardiovascular side-effects, malignancies, melanomas and neurological defects.

Here, I have reviewed the most recent long-term ($\geq$12 months) clinical data for biological agents (etanercept, infliximab, adalimumab, and ustekinumab) that have been approved for the treatment of adults with moderate-to-severe plaque psoriasis.

Table 1. Overview of reported important side effects of biologics

	Etanercept	Infliximab	Adalimumab	Ustekinumab
Common side effects	• URTI • Injection site reactions • Pruritus	• URTI • Acute infusion reaction • Headache • Pruritus • Urticaria • Transaminases	• URTI • Injection site reactions • Headache	• URTI • Headache
Uncommon but severe side effects	• Severe infections • Opportunistic infections • Reactivation of latent TB or progression of recently acquired TB • New onset or exacerbation of CNS demyelinating disorders • Possible increased risk of malignancy (in particular lymphoma) • Drug-induced lupus • Exacerbation of CHF • Vasculitis • Aplastic anaemia	• Severe infections • Opportunistic infections • Reactivation of latent TB or progression of recently acquired TB • New onset or exacerbation of CNS demyelinating disorders • Possible increased risk of malignancy (in particular lymphoma) • Drug-induced lupus • Exacerbation of CHF • Vasculitis • Pancytopenia	• Severe infections • Opportunistic infections • Reactivation of latent TB or progression of recently acquired TB • New onset or exacerbation of CNS demyelinating disorders • Possible increased risk of malignancy (in particular lymphoma) • Drug-induced lupus • Exacerbation of CHF • Vasculitis	• Severe infections • Possible reactivation of latent TB or progression of recently acquired TB • Possible increased risk of malignancy • Myocardial infarction/Stroke

(1) Common side effects
- · significantly higher than placebo, but mostly well tolerated or manageable
- · patients should be fully informed of the risks of their treatments and believe that they have a significant input into their treatment plan

(2) Major adverse cardiovascular events
- · no significant difference in frequency
- · but still, attention should be paid to these pre-existent cardiovascular risk factors

(3) Malignancies
- · potential risk of melanoma, NMSC and non-skin malignancies in patients treated with biologics has been raised by several case reports
- · close monitoring still required before and during the use of biologics

(4) Hepatitis
- · use of biologics limited in patients with chronic infections such as HBV and HCV
- · guidelines recommend to avoid biologics in chronic hepatitis B carriers because of the risk of reactivation
- · data for hepatitis C less clearcut than hepatitis B
- · may allow for the use of etanercept in patients with hepatitis C, provided patients are appropriately monitored during treatment

(5) Tuberculosis
- · agents that block TNF → ↑ reactivation of latent infections such as tuberculosis
- · TB screening before use of TNF inhibitors and also ustekinumab
- · successfully minimized with adequate prophylaxis

(6) Other serious infections
- · no clear association between biologic treatment and an increased risk of serious infection
- · special attention needed in patients on other immunosuppressive agents or had concomitant factors associated with immunosuppression

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S2-3 / Invited Lecture

What should we do, when one biologic fails?

Tomotaka MABUCHI

Department of Dermatology, Tokai University School of Medicine, Kanagawa, Japan

The patients with psoriasis can be treated with two or three anti-TNFα agents and one anti-IL-12/23p40 agent in Korea and Japan. Although these biologic agents have dramatic effects for moderate to severe psoriasis, it's not uncommon to observe no or lack of response to a biologic agent in a patient with psoriasis. What should we do, when one biologic fails? Should we switch a biologic agent to the other agent immediately after one biologic fails?

There are two important factors in treatment failure of biologics. One is development of neutralizing antibodies, the other is lower drug concentration. Lower drug concentration is due to lower drug dose with/without neutralizing antibodies. To increase drug concentration, to prevent development of neutralizing antibodies, what should we do?

In this lecture, previous reports against treatment failure of biologics in treatment not only for psoriasis but also for rheumatoid arthritis and inflammatory bowel disease are shown. Moreover, I would like to show concrete measures.

Session 3

Special Lecture

CURRICULUM VITAE

Diamant THAÇI
J.W. Goethe University
Frankfurt, Germany

Diamant Thaçi is currently working as Head of the Phototherapy Division and Director of Clinical Research in the Department of Dermatology and Venereology of J.W. Goethe University in Frankfurt, Germany. He graduated from the University of Pristina in Kosovo as a medical doctor. He worked as a resident at the Department of Dermatology and Venereology at the University of Pristina, and at the Department of Dermatology and Venereology at the J.W. Goethe University. Since 1995, Prof Thaçi has been a board-certified dermatologist.

Professor Thaçi received the Theodor Stern Foundation Award for excellence in clinical research and the European Academy of Dermatology and Venerology Award 2008 for his oral presentation. He is a member of the international Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). He has also published several articles in dermatology journals, including the British Journal of Dermatology, the Journal of the American Academy of Dermatology, the Journal of Investigative Dermatology, Dermatology, and Archives of Dermatological Research.

Professor Thaçi's main areas of interest are treatment and research of chronic inflammatory skin diseases, especially psoriasis and atopic dermatitis. He has conducted many national and international studies covering topicals, systemics and biologics in anti-psoriatic treatment.

TNF- α Antagonists

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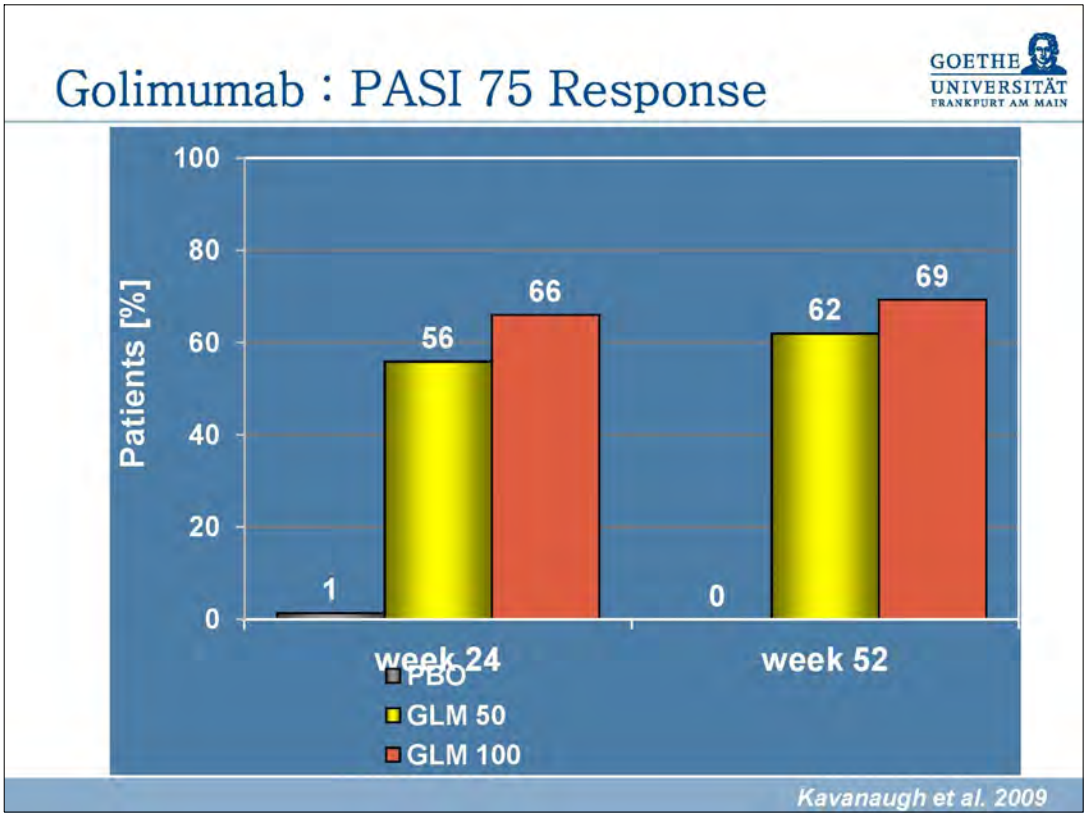
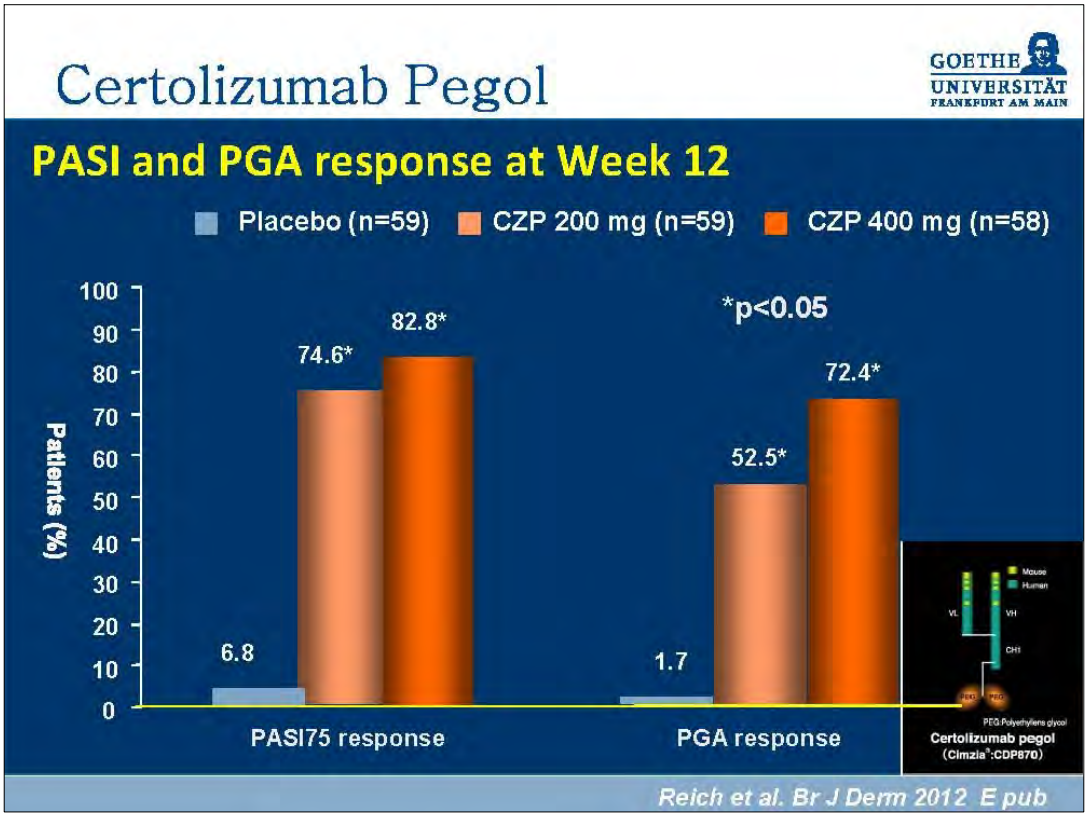
	Infliximab	Etanercept	Adalimumab	Golimumab
Design	Mouse/human chimeric mAB	Human receptor/Fc fusion protein	Recombinant human mAb	Recombinant human mAb
Isotype	IgG1	IgG1 (no CH1 domain)	IgG1	IgG1
Structure				
How generated	Engineered murine mAb	TNF RII (p75) extracellular Domain fused to F c	Murine mAb, phage display, affinity maturation	Medarex HuMab transgenic mouse
How produced	Murine myeloma cells	Chinese hamster ovary cells	Chinese hamster ovary cells	Murine myeloma cells
How supplied	Lyophilized, 100 mg/vial	Liquid, 50 mg/mL in prefilled syringe, autoinjector	Liquid, 40 mg/mL in prefilled syringe, autoinjector	Liquid, 50 mg/mL & 100 mg/mL in prefilled syringe, autoinjector
Specificity	TNF-α	TNF-α/LT	TNF-α	TNF-α
Frequency	q8 weeks	qw	q2 weeks	Q monthly
Half-life	8-10 days	3-5.5 days	10-20 days	12 days


Golimumab : PASI 75 Response
GOETHE UNIVERSITÄT FRANKFURT AM MAIN
Patients [%]
100
80
60
40
20
0
1
56
66
0
62
69
week 24
week 52
PBO
GLM 50
GLM 100
Kavanaugh et al. 2009


Certolizumab Pegol
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PASI and PGA response at Week 12
Placebo (n=59)
CZP 200 mg (n=59)
CZP 400 mg (n=58)
Patients (%)
100
90
80
70
60
50
40
30
20
10
0
6.8
74.6*
82.8*
*p<0.05
1.7
52.5*
72.4*
PASI75 response
PGA response
Mouse
Human
VL
VH
CH1
PEG:Polyethylene glycol
Certolizumab pegol
(Cimzia®;CDP870)
Reich et al. Br J Derm 2012 E pub

Briakinumab versus Etanercept and Placebo
PASI 75 Response at Week 12

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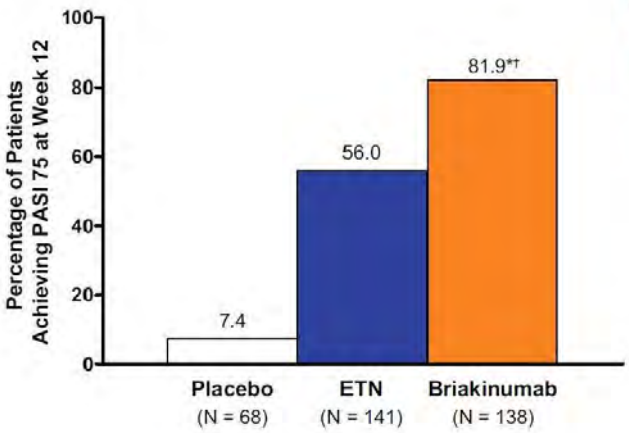

*P<0.001, briakinumab vs. placebo
†P<0.001, briakinumab vs. ETN
NRI

A. Gottlieb. Presented at the EADV in Gothenburg 6-10 October 2010

Briakinumab Phase III
Briakinumab 100 mg q4w / 100 mg q12w / placebo

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	Induction Phase		Maintenance Phase		
	ABT-874 (N=981)	Placebo (N=484)	ABT-874 q4 (N=297)	ABT-874 q12 (N=298)	Placebo (N=149)
Any AE	**517 (52.7)**				
Any AE leading to discontinuation of study drug	**17 (1.7)**				
Any serious AE	**20 (2.0)**				
Deaths	**1**				
AEs of special interest:					
Any infecton	**219 (22.3)**				
Serious infections	**5 (0.5)**				
Malignancies	**6 (0.6)**				
SCC	**4 (0.4)**				
BCC	**0**				
Other	**2 (0.2)**				
Cardiovascular	**5 (0.5)**				

Gordon K, et al. Poster presented at Winter CDC, 2010

What is MACE?

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Major

Adverse

Cardiovascular

Event

a composite end point of myocardial infarction, cerebrovascular accident, or cardiovascular death

IL12/23 inhibitors and cardiovascular ischemic risk: Points for discussion

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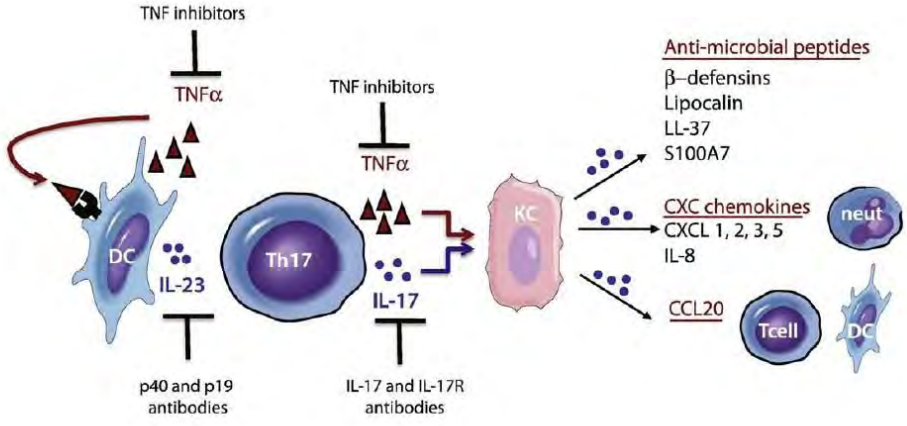
- Is the imbalance in MACE with briakinumab only observed in the induction phase ?
- Does the imbalance in MACE observed for ustekinumab and briakinumab in placebo-controlled phase reflect a class-dependent effect?
- If yes, what is the biological rationale?
- The dual function of cytokines/cellular subsets related to IL12/23p40 should be taken into account
- Are there early markers of cardiac injury ?

Anti-cytokine therapies developed for psoriasis

Generic (trade) name	Cytokine target	Status
~~Briakinumab/ ABT-874~~	IL-12 and IL-23 p40	In clinical trials
CNTO 1959 ★	IL-23 p19	In clinical trials
SCH 900222 ★	IL-23 p19	In clinical trials
~~MEDI-545~~	IFN-α	Phase 1 completed; no clinical activity in established disease [13]
~~ABX-IL8~~	IL-8	Modest results in Phase 2 trial [26]; sponsor discontinued further development for psoriasis
AIN 457 ★	IL-17	In clinical trials
LY 2439821 ★	IL-17	In clinical trials
AMG 827 ★	IL-17 receptor	In clinical trials
ILV 095	IL-22	In clinical trials
NN 8226	IL-20	In clinical trials

Kristine E. Nograles, James G. Krueger 2011; 317: 1293-1300

Anti-cytokine therapies developed for psoriasis



Kristine E. Nograles, James G. Krueger 2011; 317: 1293-1300

Biologics in der klinischen Entwicklung für Psoriasis

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Company	Agent	Target	Indications	Stage
Eli Lilly	Ixekizumab, (LY2439821)	IL-17A	Psoriasis Rheumatoid arthritis	Phase 3 Phase 2 complete
Novartis	Secukinumab (AIN457)	IL-17A	Psoriasis Rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis Non-infectious uveitis Asthma Multiple sclerosis	Phase 3 Phase 3 Phase 3 Phase 3 Phase 3 terminated Phase 2 Phase 2
Amgen/ MedImmune	Brodalumab (AMG 827)	IL-17 receptor	Psoriasis Psoriatic arthritis Rheumatoid arthritis Asthma Crohn's disease	Phase 2 complete Phase 2 Phase 2 Phase 2 Phase 2 suspended
Janssen Biotech (J&J)	Stelara (ustekinumab) (CNTO 1275)	p40 subunit of IL-23 and IL-12	Psoriasis Crohn's Ankylosing spondylitis	Approved 2009 Phase 3 Phase 2
Merck	MK-3222 (SCH 900222)	p19 subunit of IL-23	Psoriasis	Phase 2 complete
Janssen Biotech (J&J)	CNTO 1959	p19 subunit of IL-23	Psoriasis	Phase 2
Amgen/ MedImmune	AMG 139	p19 subunit of IL-23	Crohn's	Phase 1

Sources: http://www.clinicaltrials.gov/, interviews with companies, company press releases.

Ken Garber: nature biotechnology vol. 30 nr. 6 JUNI 2012

IL-17 und Psoriasis

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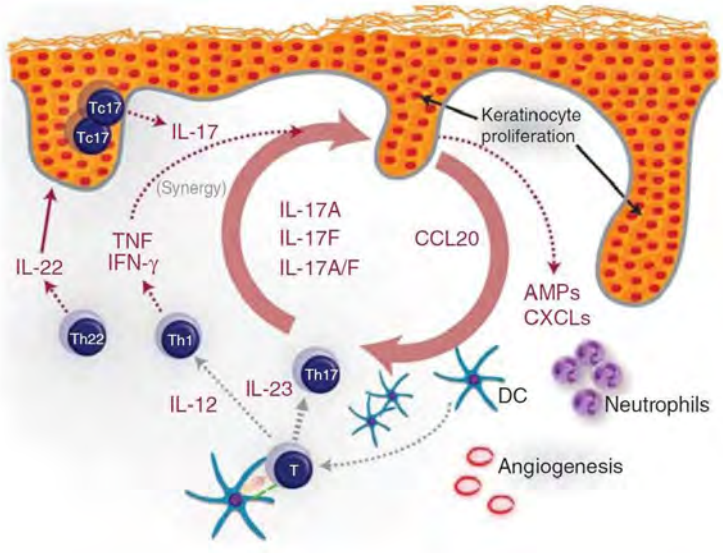
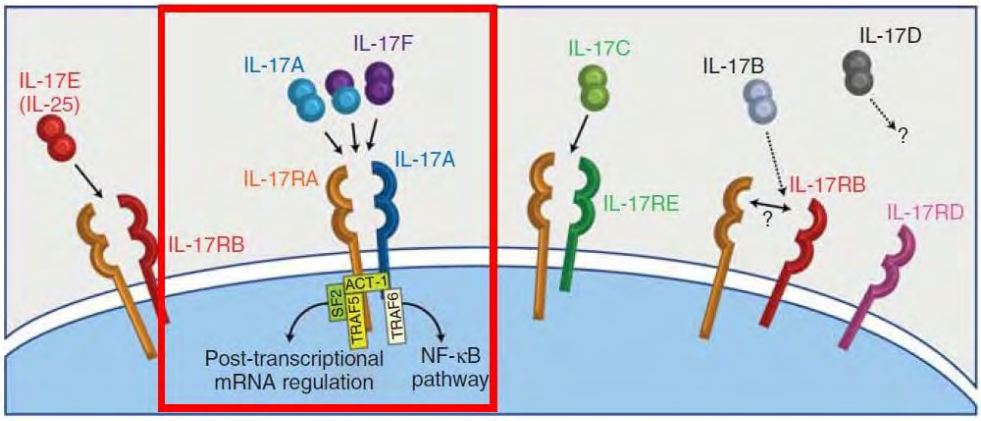


DA Martin et al.: Journal of Investigative Dermatology advance online publication, 7 June 2012

IL-17 und Psoriasis



DA Martin et al.: Journal of Investigative Dermatology advance online publication, 7 June 2012

To Be 17 Again···

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

To Be 17 Again — Anti–Interleukin-17 Treatment for Psoriasis

Ari Waisman, Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

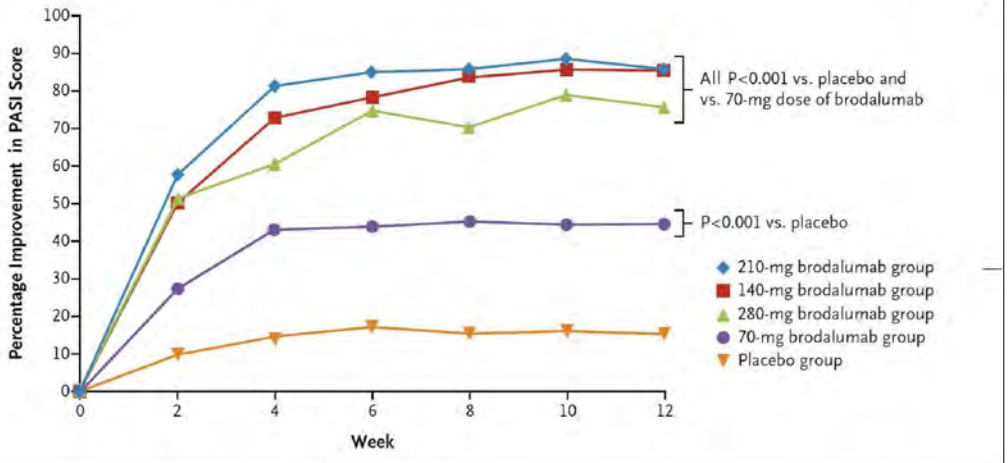


Figure 1. Percentage Improvement in PASI Scores over Time.
The P value for the comparison of the 70-mg dose of brodalumab with placebo (P<0.001) is for all the time points except week 2, for which the P value was 0.002. PASI denotes psoriasis area-and-severity index.

Papp et al. N Engl J Med 2012;E-pub Mar

Anti–Interleukin-17 : Ixekizumab

GOETHE UNIVERSITÄT FRANKFURT AM MAIN

The NEW ENGLAND JOURNAL of MEDICINE

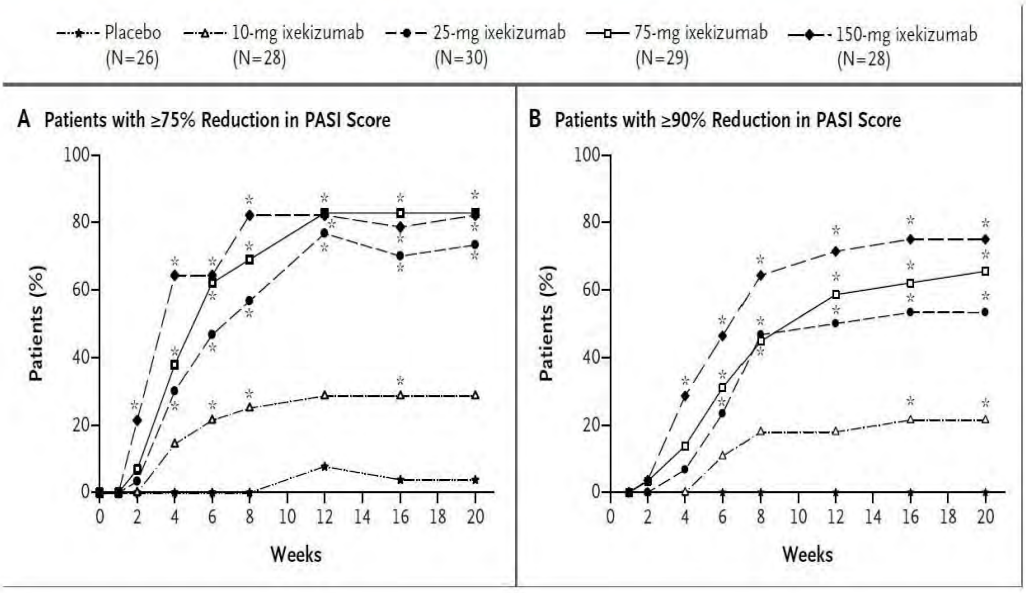
ORIGINAL ARTICLE

Anti–Interleukin-17 Monoclonal Antibody Ixekizumab in Chronic Plaque Psoriasis

Craig Leonardi, M.D., Robert Matheson, M.D., Claus Zachariae, M.D., D.M.Sci., Gregory Cameron, Ph.D., Linda Li, M.S., Emily Edson-Heredia, M.P.H., Daniel Braun, M.D., Ph.D., and Subhashis Banerjee, M.D.

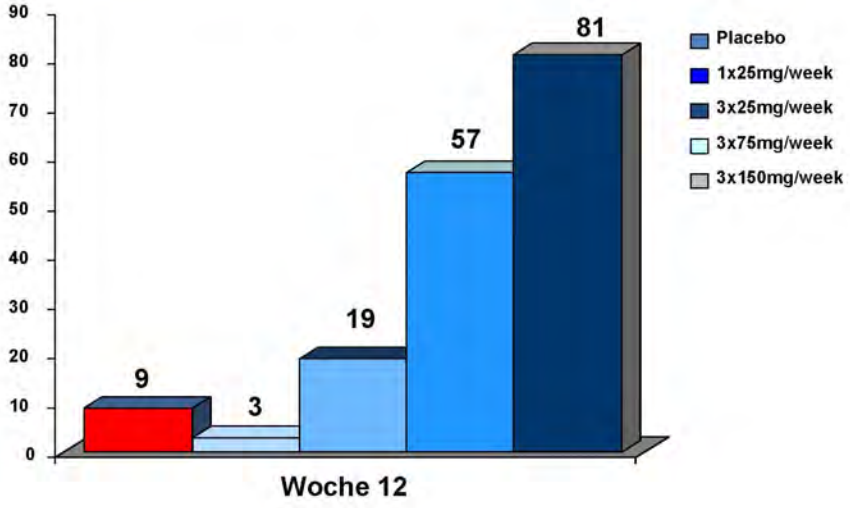
Leonardi et al. N Engl J Med 2012;366:1190-9.

Anti-Interleukin-17 : Ixekizumab Phase II PASI75/90



Leonardi et al. N Engl J Med 2012;366:1190-9.

Secukinumab IL17- PASI 75 responder rate



Abstract FC01.7 Papp et al. EADV 2011

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Beginning of a new generation of immunosuppressive therapies (safe and effective?)

Apremilast : PSOR-005 study/ PASI-75 Week 16

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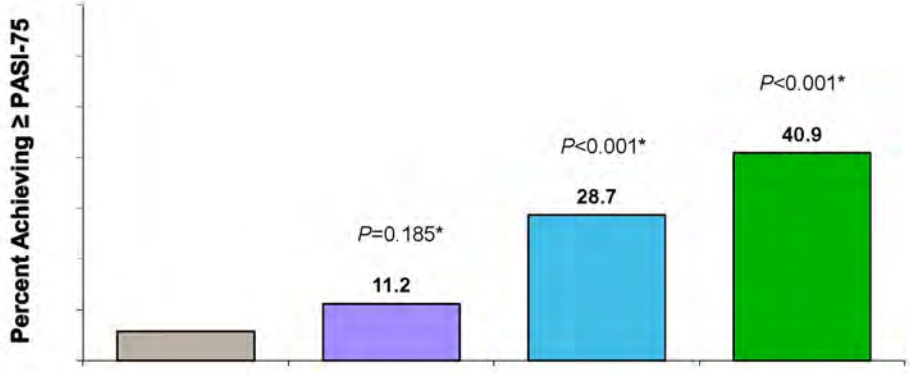
Intent-to-Treat Population (LOCF); N=352



*Versus placebo.

Apremilast is an investigational drug and is not approved for use.

LOCF=last observation carried forward; PASI-75=≥75% reduction from baseline Psoriasis Area and Severity Index.

Papp K, et al. Presented at the 41st Annual European Society for Dermatological Research Meeting, 7–10 September 2011, Barcelona, Spain.

The role of JAK pathway in immune and inflammatory response

GOETHE UNIVERSITÄT FRANKFURT AM MAIN

Multiple cytokine families signal through combinations of JAKs and STATs

STAT	JAK3	JAK1	JAK2	Tyk2	
5	IL-7 IL-9 IL-15 IL-2	IL-7 IL-9 IL-15 IL-2			Adaptive Immunity
6	IL-4	IL-4			
1, 3	IL-21	IL-21			
4			IL-12	IL-12	Inflammatory T cell Differentiation
3			IL-23	IL-23	
1, 3		IFN-γ IL-22 IL-27	IFN-γ	 IL-22 IL-27	
3		IL-10		IL-10	
1, 3		IL-6 G-CSF LIF CNTF OSM IFN-α/β	IL-6 G-CSF LIF CNTF OSM	 IFN-α/β	Innate Immunity
5			EPO TPO GM-CSF IL-3		Hematopoesis

JAK associated cytokine receptors

IFN - γ

IL-12

IL-23

IL-22

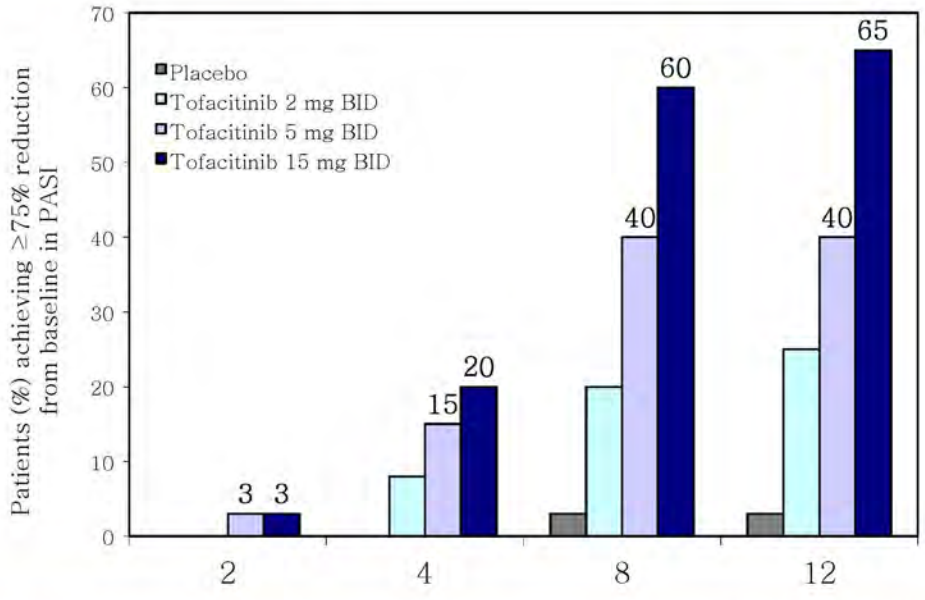
IL-2

CNTF=ciliary neurotrophic factor; G-CSF=granulocyte colony stimulating factor; EPO=erithropoetin; GM-CSF=granulocyte/macrophage colony stimulating factor; IC_{50}=half maximal inhibitory concentration; IFN=interferon; IL=interleukin; JAK=Janus kinase; LIF=leukemia inhibitory factor; OSM=oncostatin M; STAT=signal transducer and activator of transcription; TPO=thrombopoietin; Tyk2=tyrosine kinase 2.

Leonard WJ. *Nat Rev Immunol.* 2001;1:200-208.

Tofacitinib (CP-690,550), in Moderate-to-Severe Psoriasis -PASI 75 in phase II

GOETHE UNIVERSITÄT FRANKFURT AM MAIN



Jane Harness et al. AAD 2011 P3318

Conclusions

GOETHE UNIVERSITÄT FRANKFURT AM MAIN

- Our understanding of the pathophysiology of skin diseases has changed greatly in the recent past and new observations are being made that alters our theories about the disease
- As we learn more about pathophysiology, we will have a better grasp on options for therapy
- New anti-inflammatory treatments will continue to be developed with expanding efficacy and safety

Session 4

Field experiences with biologics

CURRICULUM VITAE

Jee-Ho CHOI, M.D., Ph.D.
Department of Dermatology, Asan Medical Center,
University of Ulsan College of Medicine,
Seoul, Korea

Education:

M.D.: College of Medicine, Seoul National University, Seoul, Korea (February 1981)
Ph.D.: Graduate School, Seoul National University, Seoul, Korea (February 1986)
Residency: Department of Dermatology, Seoul National University Hospital, Seoul, Korea (March 1982-February 1985)
Research Fellow: Department of Dermatology, University of Michigan, Medical Center, Ann Arbor, Michigan, U.S.A. (September 1994-August 1995)

Teaching Appointments:

2004-2010: Chairman, Department of Dermatology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
2001-present: Professor, Department of Dermatology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Memberships:

- Korean Dermatological Association (KDA) since 1985
  - Director of Scientific & Academic Committee (2005-2007)
  - Director of Board Certification Examination Committee (2007-2009)
- Korean Society for Investigative Dermatology (KSID) since 1994
  - Director of Scientific & Academic Committee (2003-2005)
  - Secretary General (2005-2007)
- Korean Society for Immuno-Dermatology (KSI) since 2005
  - Secretary General (2005-2012)
  - President (2012-present)
- Korean Society for Psoriasis (KSP) since 1997
  - Director of Scientific & Academic Committee, 1997-2002
  - Secretary General (2002-2007)
  - President (2007-2011)

CURRICULUM VITAE

Sang-Woong YOUN, M.D., Ph.D.
Department of Dermatology, Seoul National University College of Medicine
Seoul National University Bundang Hospital

Education:

1987-1993	Bachelor of Medicine, Seoul National University College of Medicine, Seoul, Korea
1995-1997	Master of Medicine, Postgraduated school of Medicine, Seoul National University, Seoul, Korea (major: Dermatology)
2001-2003	Ph.D. Postgraduated school of Medicine, Seoul National University, Seoul, Korea (major: Dermatology)

Appointment:

2002-2003	Instructor, Department of Dermatology, Seoul National University Hospital
2003-2008	Assistant professor, Department of Dermatology, Seoul National University Bundang Hospital
2004-2008	Assistant Professor, Department of Dermatology, Seoul National University College of Medicine
2007-2008	Visiting scholar, Division of Dermatology, University of California, San Diego
2008-present	Associate professor, Department of Dermatology, Seoul National University College of Medicine, Seoul National University Bundang Hospital

Memberships & Career:

2012.1-present	Director of Planning, Korean Society for Psoriasis

Specialities:

Acne
Psoriasis
Bioengineering of skin: development of objective diagnostic methods of skin disease
Cosmetic Dermatology

CURRICULUM VITAE

Tomotaka MABUCHI, M.D., Ph.D.
Department of Dermatology, Tokai University School of Medicine
Kanagawa, Japan

Education and Experiences:

1993-1999	Medical Student: Tokai University School of Medicine, Kanagawa, Japan
1999-2001	Resident: Tokai University Hospital, Kanagawa, Japan
2001-2005	Postgraduate Student: Postgraduate School of Internal Medicine (Dermatology), Tokai University School of Medicine, Kanagawa, Japan
2005-2007	Instructor: Department of Dermatology, Tokai University School of Medicine, Kanagawa, Japan
2008-2012	Assistant Professor: Department of Dermatology, Tokai University School of Medicine, Kanagawa, Japan
2009-2011	Research Fellow: Department of Dermatology, Medical College of Wisconsin, Wisconsin, USA.
2012-	Associate Professor: Department of Dermatology, Tokai University School of Medicine, Kanagawa, Japan

Awards:

2008	The best paper of the year of the Tokai Journal of Experimental and Clinical Medicine
2011	The research encouragement award of Torii/Teikoku 2011 from the Japanese Society for Psoriasis Research
2012	The research encouragement award of Torii/Teikoku 2012 from the Japanese Society for Psoriasis Research

CURRICULUM VITAE

Jae-We CHO, M.D., Ph.D.
Department of Dermatology, Keimyung University School of Medicine, Daegu, Korea

Education:

1996 M.D., School of Medicine, Keimyung University
2001 Ph.D., Postgraduate School of Medicine, Keimyung University

Appointment:

2009-2011 Assistant Professor, Department of Dermatology, Keimyung University
2012-present Associate Professor, Department of Dermatology, Keimyung University

Professional Experiences:

August 2007 Visiting Research track, Osaka University, Division of Gene Therapy Science; Bone marrow stem cell application to
Feb 2013 Visiting Scholar, Tokyo University adipose tissue derived stem cell application to

Memberships:

Korean Dermatological Association
Korean Society for Psoriasis
Korean Society for Atopic Dermatitis
Korean Society for Investigate of Dermatology
Korean Society for Photomedicine