Symposium 4: Psoriasis

◎ Topic: Oral systemic therapy for Psoriasis: Now & from now on

◎ Background for the topic: : Psoriasis is a chronic inflammatory disorder mainly affecting skin, but it also affects internal organs and has lots of systemic comorbidities. Patients with severity more than moderate psoriasis should be treated with systemic treatment modalities. Conventional oral systemic agent has been a main axis of the management of moderate to severe psoriasis. Oral retinoids was the most commonly prescribed medication for moderate to severe psoriasis. Nowadays, due to the introduction of biologics and its insurance guidelines, the importance of cyclosporine or methotrexate are increasing. Cyclosporine was introduced as a systemic agent for psoriasis more than 20 years. But, we do not know much about cyclosporine used for Korean psoriasis patients. Fumaric acid is an old psoriasis drug, mainly has been used in Germany. In European countries, fumaric acid arouse many psoriasis doctor's interest because it has different adverse effect profile than conventional oral medications. It is worth that psoriasis doctors should pay attention on this medication. Apremilast, a PDE4 inhibitor, is currently the main oral systemic medication for psoriasis in US. It shows relatively low possibility of renal impairment which is the major concern of cyclosporine, and low incidence of hepatic dysfuction.

In this session, we will suggest the past, current, and the future perspectives of oral medications for psoriasis by presenting the representative medications as cyclosporine, fumaric acid, and apremilast

◎ Program director: Sang Woong Youn (Academic Director)

◎ Format: Lecture (O), Panel Discussion ( ), Workshop ( ), the others ( )

Symposium 4-2 (SYP 4-2)

Cyclosporine: now it is a famous medication for psoriasis

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Cyclosporine (CsA) is an immunosuppressant or immunomodulator for various chronic dermatosis. It binds to cyclophilin, and CsA/cyclophilin complex inhibits calcineurin, which is responsible for activating transcription of interleukin 2. The first report of CsA for the application to psoriasis was published in 1979, the firstly described dosage was the same with anti-transplanation rejection.

(1) CsA the dosage for psoriasis: 3-5mg/kg/D.

1) short term therapy
   - induction within 10-16 wk.
   - abrupt discontinuation: higher relapse rate
2) long term therapy
   - maintenance therapy
   - initial 3-5mg/kg/D, after remission decrease every 2 wks
   - relapse: increase dose again

(2) Contraindication of CsA

1) impaired renal function
2) insufficiently controlled hypertension
3) severe infection
4) history of malignancy
5) simultaneous PUVA therapy

(3) important side effects

very frequent	none
frequent	renal failure, irreversible renal damage, hypertension, gingival hyperplasia, reversible hepatogastric complaints, tremor, burning sensation of hands & feet, reversible elevated blood lipids, hypertrichosis
occasional	seizures, GI ulceration, weight gain, hyperglycemia, hyperuricemia, hyperkalemia, hypomagnesemia, anemia
rare	ischemic heart disease, pancreatitis, motor polyneuropathy, impaired vision, defective hearing, central ataxia, thrombocytopenia
very rare	microangiopathic hemolytic anemia, hemolytic uremic syndrome, colitis, papillary edema, indiopathic intracranial hypertension

■ CURRICULUM VITAE ■

윤상웅(Sang Woong Youn, M.D., Ph.D.)

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Symposium 4-3 (SYP 4-3)

Fumaric acid for psoriasis

Yu Sung Choi, M.D., Ph.D.

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Fumaric acid esters (FAE) are small molecules which introduced as a systemic psoriasis treatment in 1959. FAE are licensed only in Germany for the treatment of moderate-to-severe psoriasis. To date, there is no European Medicines Agency or US Food and Drug Administration (FDA) approved use of FAE in psoriasis patients. Despite this, FAE are increasingly being used as an unlicensed treatment in several European countries and are recommended in the European guidelines for the management of moderate to severe plaque psoriasis.

1. History

In 1959, the German chemist Walter Schweckendiek postulated that psoriasis occurred due a deficiency of fumaric acid levels leading to defects in the citric acid cycle, and that oral supplementation of fumaric acid might neutralize these defects. In the 1970s the German general practitioner Gunther Schaefer standardized oral and topical application of FAE in combination with a diet. In the early 1990s, the first randomized placebo-controlled trial that evaluated FAE in psoriasis was published, in which efficacious response and good safety profile were observed in patient with chronic plaque psoriasis. Following theses clinical trials, FAE treatment became approved in 1994 in Germany for systemic treatments of severe psoriasis in adult.

2. Mechanism of action

The mechanisms of action by which FAE improve psoriasis are not yet completely understood. FAE are thought to elicit their effects through multiple immunomodulating effects. Recent experimental studies have described various immunomodulatory effect including anti-inflammatory, and anti-oxidative properties of FAE.

3. Safety and adverse effects

Adverse events
Subjective adverse events
Gastrointestinal complaints
Skin flushing
Pruritus
Headache
Fatigue
Lower extremity edema
Laboratory adverse events
Decrease in lymphocyte count
Increase in eosinophil count
Proteinuria
Increase of serum creatinine
Increase of ASAT/ALAT

Abbreviations: ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; RCT, randomized controlled trial; FAE, fumaric acid esters.

4. Efficacy of FAE

A. Observational studies

B. Randomized controlled trials(Table 1)

5. Guidelines for FAE treatment in psoriasis

The recommended indication of FAE is the treatment of moderate-to-severe plaque psoriasis. Contraindications of FAE are severe gastrointestinal and renal disease, pregnancy and breastfeeding. Dosing regimen of FAE as recommended the European S3-guidelines on psoriasis treatment.

Week	No of tablets per day 105 mg	No of tablets per day 215 mg
Week 1	1	–
Week 2	2	–
Week 3	3	–
Week 4	–	1
Week 5	–	2
Week 6	–	3
Week 7	–	4
Week 8	–	5
Week 9	–	6

6. Summary of clinical response and recommendations regarding FAE in the treatment of plaque psoriasis

No of studies	Six RCTs, 29 observational studies, 3,439 patients
PASI-75 response at week 16	50%–70% of patients
Withdrawal rate due to adverse events	6%–40% of patients
Speed of onset	First clinical response week 6 of treatment
Indications	Moderate-to-severe plaque psoriasis
Contra-indications	Severe gastrointestinal disease, severe renal disease, pregnancy, and lactation
Maximum dosage	Six tablets 215 mg per day (720 mg DMF)
Mean dosage	One to three tablets 215 mg per day (120–360 mg DMF)
Common adverse events	Gastrointestinal complaints, flushing, lymphocytopenia, eosinophilia, and proteinuria
Monitoring	Leukocyte counts, serum creatinine, ASAT/ALAT, and urinalysis
Drug interactions	No known drug interactions

Abbreviations: ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; DMF, dimethyl fumarate; FAE, fumaric acid esters; RCTs, randomized controlled trials; PASI, psoriasis area and severity index.

Reference

1. Balak DM, Fallah Arani S, Hajdarbegovic E et al. Efficacy, effectiveness and safety of fumaric acid esters in the treatment of psoriasis: a systematic review of randomized and observational studies. Br J Dermatol. 2016;175:250-262
2. Atwan A, Ingram JR, Abbott R et al. Oral fumaric acid esters for psoriasis: abridged Cochrane systematic review including GRADE assessments. Br J Dermatol. 2016;175:873-881
3. Wain EM, Darling MI, Pleass RD et al. Treatment of severe, recalcitrant, chronic plaque psoriasis with fumaric acid esters: a prospective study. Br J Dermatol. 2010;162:427-434

■ CURRICULUM VITAE ■

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Education:

1996-2001	Konyang University College of Medicine (MD), Daejeon, Korea
2010	Korea University Graduate school of Medicine (Ph.D), Seoul, Korea

Training and Fellowship Appointments:

2002-2003	Internship, National Medical Center, Seoul, Korea
2003-2007	Dermatology residency, National Medical Center, Seoul, Korea
2007-2008	Fellowship, Seoul National University Hospital, Seoul, Korea

Faculty Appointment:

2008-2011	Clinical Assistant Professor, Ulsan University Hospital, Ulsan, Korea
2012-2017	Assistant Professor, Ulsan University Hospital, Ulsan, Korea
2017-	Associate Professor, Ulsan University Hospital, Ulsan, Korea

Memberships:

2007-	Korean Dermatological Association
2015-	Director of Planning, Korea Society for Acne Research
2017-	Director of Promotion, Korean Society for Psoriasis
2017-	Director of Publication, Korean Society of Skin Cancer

Symposium 4-4 (SYP 4-4)

Apremilast: is it a promising oral medication for psoriasis?

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- Apremilast: Oral, small-molecule phosphodiesterase-4 inhibitor
- Mode of action: Anti-inflammatory rather than immunosuppressive
- Approved for adults with psoriasis and psoriatic arthritis in 2014(FDA), 2015(EU), 2017(KFDA)
- Key phase III clinical trial

Psoriasis	Treatment	PASI75 (%) at week 16
ESTEEM-1 (n=844)	Apremilast vs. Placebo	33.1 vs. 5.3
ESTEEM-2 (n=413)		28.8 vs. 5.8
LIBERATE (n=250)	Apremilast vs. Etanecept vs. Placebo	39.8 vs. 48.2 vs. 11.9
Psoriatic arthritis	**Treatment**	**ACR20 (%) at week 16**
PALACE-1 (n=504)	20mg APR vs. 30mg APR vs. PBO	30.4 vs. 38.1 vs. 19.0 63.0 vs. 54.6. (week 52)
PALACE-2 (n-484)		37.4 vs. 32.1 vs. 18.9
PALACE-3 (n=505)		28.0 vs. 41.0 vs. 18.0
PALACE-4 (n=527)		28.0 vs. 30.7 vs. 15.9 vs. 58.0 (week 52)

- Advantage
  ① Convenient twice-daily oral administration and dosing
  ② Favorable safety profile
    - No need of lab prescreening or ongoing monitoring for laboratory parameters
    - Diarrhea and nausea (usually resolving within 4 weeks)
    - No identified risk of tuberculosis or opportunistic infections in clinical trials
  ③ Efficacy in difficult-to treat forms, including nail, scalp and palmoplantar manifestations
- Disadvantage
  ① Moderate efficacy compared with biologics for both psoriasis and psoriatic arthritis
  ② Uncertain cost-effectiveness

■ CURRICULUM VITAE ■

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Education:

1992-1998	Yonsei University College of Medicine (MD), Seoul, Korea
2007-2009	Yonsei University College of Medicine (MS), Seoul, Korea
2010-Present	Yonsei University College of Medicine (PhD), Seoul, Korea

Training and Fellowship Appointments:

1999-2003	Dermatology residency, Bundang CHA Medical Center, Seongnam, Korea
2006-2007	Research fellow, Yonsei University Hospital, Seoul, Korea
2012-2014	Skin Tissue Engineering Lab (LOEX), Laval University, Canada

Faculty Appointment:

2007-2009	Full-time instructor, Bundang CHA Medical Center, Seongnam, Korea
2009-2014	Assistant professor, Dermatology, CHA University College of Medicine
2014-Present	Associate professor, Dermatology, CHA University College of Medicine

Memberships:

2003-present	Korean Dermatological Association
2014-present	Korean Society of vitiligo
2014-present	Korean Society of Dermatopathology
2014-present	Korean Society of Pigment Cell Research
2015-present	Korean Society for psoriasis