

Safe Use of Systemic Agents in Dermatology

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Disclosure (previous 12 months)

- **Consultant –Eli Lilly, Celgene, Castle Biosciences, XOMA, Pfizer, Biogen/IDEC, Elekta, Leo Pharma, Janssen Biotech, Abbvie**
- **Editorial Boards – UpToDate (editor-in-chief, Dermatology), JAMA Dermatology (Associate Editor), Journal Watch Dermatology (Deputy Editor), Journal of Rheumatology, Cutis, emedicine.com, Journal of Drugs in Dermatology, Journal of the European Academy of Dermatology and Venereology, Medicine, Psoriasis Forum, Australasian Journal of Dermatology**
- **I will discuss “off-label” uses of some of the currently available agents and will identify which are labeled v. off-labeled uses.**

April 2016

Malkinson Lecture

Chicago Dermatological Society



- He was the founder of the Department of Dermatology at Rush
- Editor in Chief of Yearbook of Dermatology and Archives of Dermatology
- Established the NRMP match for dermatology residents in 1982
- He was president of the Chicago Literary Club

Learning Objectives

- **Following this lecture the attendee will be able**
 - **To list the risks of some “traditional” systemic therapies used in dermatology**
 - **Discuss their potential mechanism of action**
 - **Select an appropriate therapy for patients; and**
 - **Design a method for monitoring patients before and during therapy**

Topics for Discussion

- **General approach to selection of therapy**
- **Antimalarial therapy**
- **Traditional immunosuppressive agents**
 - **Methotrexate**
 - **Azathioprine**
 - **Mycophenolate mofetil**

Questions prior to selection of a systemic therapy

- **Is the diagnosis correct?**
- **Is the process reversible or controllable?**
- **Are there other factors that might impact your selection of an agent?**
 - **Potential drug interactions?**
 - **Patient or disease characteristics?**
- **Know the risks and benefits of the agent you will use, and document your discussion.**

Which Agent to Use & When to Use It

- **Ideally, it would be nice if an agent was selected based upon knowledge of the mechanism of action and the pathogenesis of the disease**
- **Unfortunately, most of our current knowledge is based upon observation or individual cases or small case series**

Disease	Agents recommended
Psoriasis	MTX, 6-TG, cyclosporine
Cutaneous LE	Antimalarials, MTX, MMF, AZA
Sarcoidosis	Antimalarials, MTX, AZA, MMF, adalimumab, infliximab
Chronic Eczema	AZA, MMF, cyclosporin
Pyoderma gangrenosum	AZA, MMF, adalimumab, infliximab
Cutaneous Dermatomyositis	Antimalarials, MTX, MMF, IVIG
Pemphigus	AZA, MMF, CTX, Chlorambucil, Rituximab, IVIG
Bullous pemphigoid	MTX, AZA, rituximab

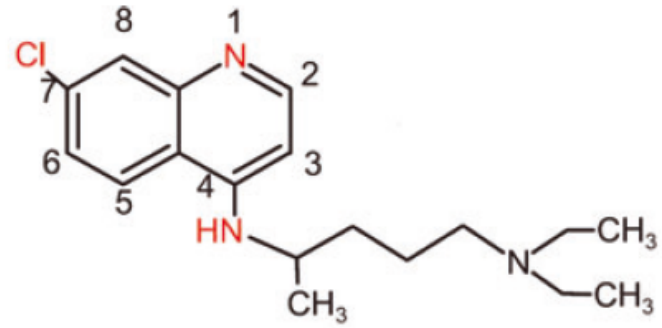
Antimalarial Therapy

History

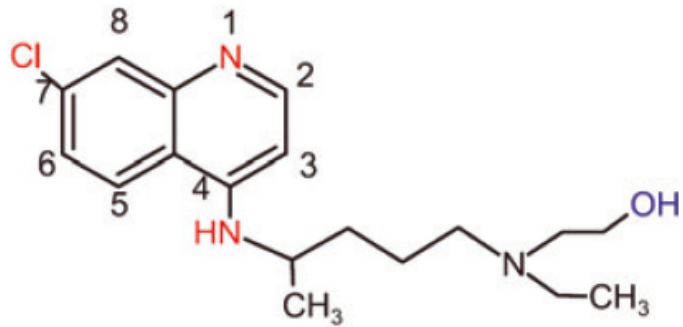
- **Centuries ago: South American cinchona tree used for antipyretic effects**
- **1800s: Quinine used as an antimalarial**
 - 1894 quinine used to treat lupus erythematosus
- **1930: Quinacrine hydrochloride synthesized**
- **1934: Chloroquine phosphate**
- **1946: Hydroxychloroquine sulfate**
 - 1951 case series of 17/18 DLE patients improving with quinacrine

Ochsendorf FR. Use of antimalarials in dermatology, JDDG 2010
Callen JP, Camisa C. Antimalarial agents, in Wolverton 2013

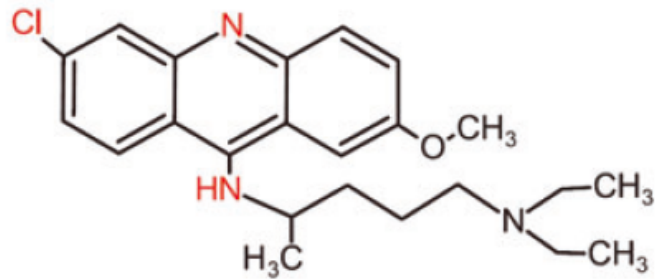
Chloroquine



Hydrochloroquine



Quinacrine



Effect	Mechanism	Results/Details
Immunomodulatory	Inhibits autoantigen processing	Diminished class II antigen presentation
	Reduced stimulation of autoreactive CD4+ T cells	
	Reduced cytokine production: of IL1, 2, 6, TNF- α by macrophages and IL1, 2, 5 by T lymphocytes	
	Sequestration of membrane particles	Diminished surface receptors ~ 50 %; and thus diminished response to mitogenic stimuli
	Binding to DNA and thus competitive inhibition of anti-DNA antibodies	
Anti-inflammatory	Inhibition of phospholipase A2 and C	Diminished arachidonic acid release and prostaglandin synthesis; reduced bradykinin effect
	Inhibition of formation of IL1beta, TNF alpha	mRNA and protein level
	Inhibition of mast cells	Diminished leukotriene synthesis and histamine release
	Inhibition of Toll-like receptor 9 signal pathway	Diminished antigen presentation and immune stimulation

Antiproliferative	Interaction with protein synthesis	Inhibition of DNA/RNA biosynthesis and polymerase
UV absorption	Increased UV filtration? (questionable relevance)	After spectral shift in relation to accumulation in melanin and increase epidermal concentrations
	Inhibition of UV-induced inflammatory reactions	Possibly due to interaction with UV-B induced C-jun transcription
Anti-infectious	Antimicrobial effects on HIV, SARS, coronavirus, influenza viruses	
Coagulation	Inhibition of thrombocyte aggregation: diminished CD41a and CD61 expression	Without prolonging time to coagulation
Metabolic	Reduced cholesterol, triglyceride, LDL levels	
	Complex formation with porphyrins	Increased excretion
	Reduced hydroxylation vitamin D	Reduction in 1,25-dihydroxyvitamin D ₃
Misc.	Increased pain threshold	Also in healthy individuals

Antimalarial Therapy

- **Indications:**
 - **Approved – LE*, RA, Malaria**
 - **Other – Sarcoidosis, dermatomyositis, polymorphous light eruption, porphyria cutanea tarda, granuloma annulare, other**
- **Available agents:**
 - **Hydroxychloroquine 200 to 400 mg/d**
 - **Chloroquine 250 to 500 mg/d**
 - **Quinacrine – 100 to 200 mg/d (must be obtained from a compounding pharmacy)**

*Antimalarial agents appear to be less effective in smokers

**The effect of increasing the dose of
hydroxychloroquine (HCQ) in patients with
refractory cutaneous lupus erythematosus
(CLE): An open-label prospective pilot study**

François Chasset, MD,^a Laurent Arnaud, MD, PhD,^{b,c} Nathalie Costedoat-Chalumeau, MD, PhD,^{d,e}
Noel Zahr, PharmD, PhD,^f Didier Bessis, MD,^g and Camille Francès, MD^a
Paris and Montpellier, France

J AM ACAD DERMATOL
■ 2015

Methods

- **Open-label prospective study 2010-2014**
- **Patients with chronic, intermittent, or subacute CLE. Confirmed with biopsy, treated with HCQ for 3+ months, CLASI greater than 2, HCQ >100 but <750 ng/mL, no change in therapy in preceding 3 mo**
- **Excluded <18 yo, prior retinopathy or HCQ side effect**
- **Every 3 months patients HCQ dose was increased until blood concentrations were at least 750ng/mL**
- **Evaluated based on CLASI, improvement was considered 20% improvement of score, followed for 6 mo**

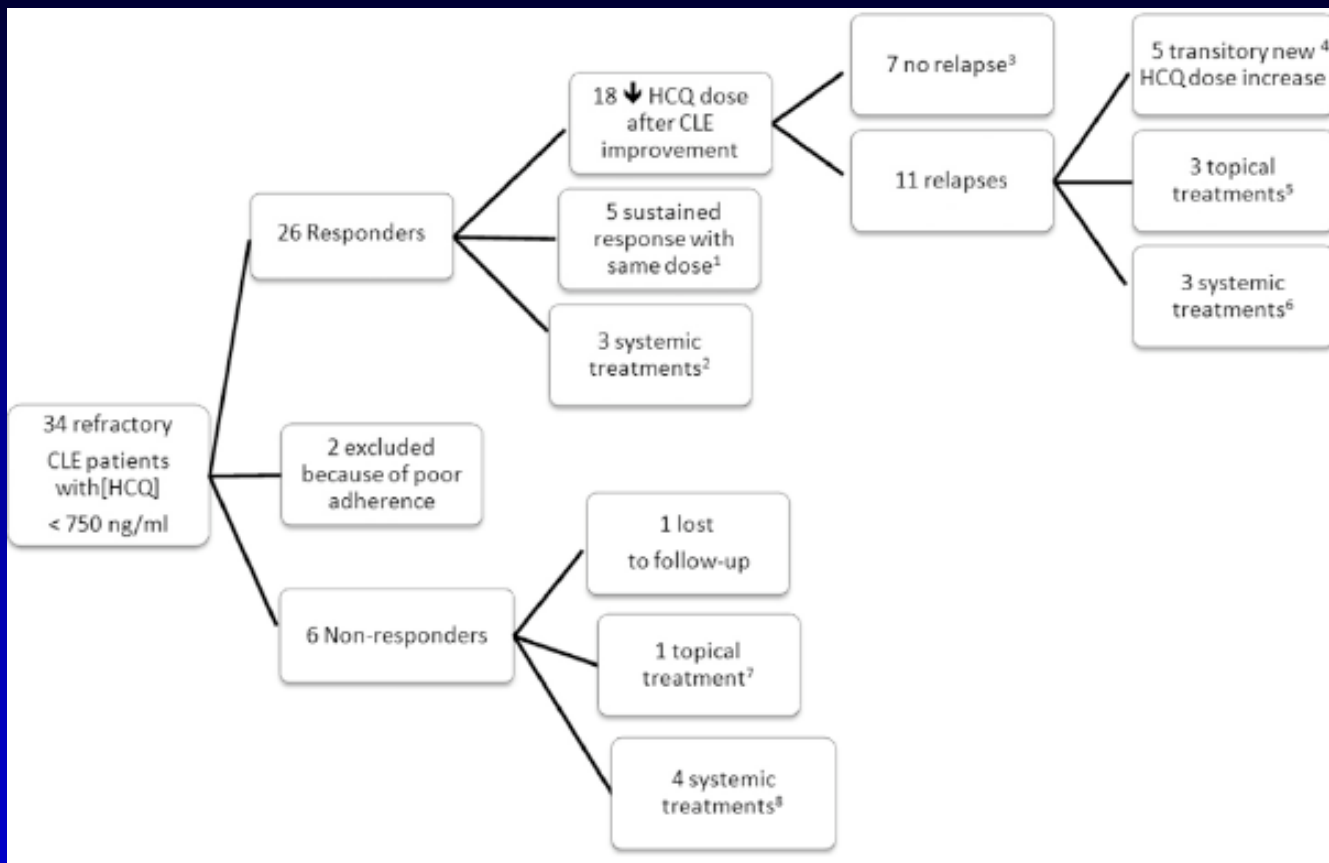
Table I. Baseline characteristics of patients with refractory cutaneous lupus erythematosus (n = 32)

Patients characteristics	
Demographic data	
Age, y, median (range)	45 (28-72)
Female, n (%)	25 (78)
CLE duration, mo, median (range)	44.9 (1.2-262)
CLE subtypes, n (%)*	
CCLE	17 (53)
DLE	17 (53)
Chilblain lupus	1 (3)
Lupus panniculitis	1 (3)
ICLE: lupus erythematosus tumidus	6 (19)
SCLE	
Annular	9 (28)
Psoriasiform	4 (12)
≥1 CLE subtype, n (%)	4 (12)
SLE (≥4 SLICC 2012 criteria), n (%)	17 (53)
Smoking status, n (%)	
Current smokers	15 (47)
Past smokers	3 (10)
Disease severity, n (%)	
Mild disease (CLASI score: 0-9)	20 (62)
Moderate disease (CLASI score: 10-20)	8 (25)
Severe disease (CLASI score: 21-70)	4 (12)
Additional therapies, n (%)	
Skin photoprotection	30 (94)
Topical corticosteroids	10 (31)
Topical tacrolimus	4 (12)
Systemic corticosteroids [†]	5 (16)
Methotrexate [‡]	2 (6)
Mycophenolate mofetil [§]	2 (6)

Table II. Impact of increasing blood hydroxychloroquine concentration above 750 ng/mL in refractory cutaneous lupus erythematosus (n = 32)

Variables, median (range)	Baseline	After HCQ dose increase	<i>P</i> value
CLASI score	8 (2-30)	1.5 (0-30)	<.001
RCLASI score	9 (4-38)	1.5 (0-38)	<.001
HCQ blood concentration (ng/mL)	638 (100-749)	1187 (760-2095)	<.001

- SCLE improved more than non-SCLE patients
- Patients with lower baseline CLASI scores achieved primary endpoint than those with higher baseline CLASI scores
- SCLE patients were less likely to have relapse after decreases dose than non-SCLE patients
- Patients that experienced a large improvement in CLASI were less likely to have relapse



Comment

- **In patients with CLE not responding to traditional doses of HCQ, especially SCLE, we should consider increasing dose of HCQ or evaluating blood concentration to ensure >750 ng/mL.**
- **It is important to note that the American Academy of Ophthalmology advocates that 6.5 mg/kg of ideal body weight is the max dose to avoid retinal toxicity.**
- **Limitations: few patients, open-label design, doesn't assess longterm retinal toxicity**

Hydroxychloroquine sulfate treatment is associated with later onset of systemic lupus erythematosus

JA James^{1,2*}, XR Kim-Howard^{1,3}, BF Bruner^{1,2}, MK Jonsson⁴, MT McClain¹, MR Arbuckle¹, C Walker⁵, GJ Dennis^{5,6}, JT Merrill⁷ and JB Harley^{1,2,8}

Systemic lupus erythematosus (SLE) is a clinically diverse, complex autoimmune disease which may present with coincident onset of many criteria or slow, gradual symptom accrual. Early intervention has been postulated to delay or prevent the development of more serious sequelae. One option for treatment in this setting is hydroxychloroquine. Using 130 US military personnel who later met ACR SLE criteria, a retrospective study of onset, development and progression of SLE with and without pre-classification hydroxychloroquine ($n = 26$) use was performed. Patients treated with hydroxychloroquine prior to diagnosis had a longer (Wilcoxon signed rank test, $P = 0.018$) time between the onset of the first clinical symptom and SLE classification (median: 1.08 versus 0.29 years). Patients treated with prednisone before diagnosis also more slowly satisfied the classification criteria (Wilcoxon signed rank test, $P = 0.011$). The difference in median times between patients who received NSAIDs before diagnosis, as opposed to those who did not, was not different ($P = 0.19$). Patients treated with hydroxychloroquine also had a lower rate of autoantibody accumulation and a decreased number of autoantibody specificities at and after diagnosis. These findings are consistent with early hydroxychloroquine use being associated with delayed SLE onset. A prospective, blinded trial testing the capacity of hydroxychloroquine to delay or prevent SLE in high risk populations is warranted. *Lupus* (2007) **16**, 401–409.

Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine

Peter M Izmirly,¹ Mimi Y Kim,² Carolina Llanos,¹ Phuong U Le,³ Marta M Guerra,³
Anca D Askanase,¹ Jane E Salmon,³ Jill P Buyon¹

Ann Rheum Dis 2010; 69:1827-30

ARTHRITIS & RHEUMATISM
Vol. 62, No. 3, March 2010, pp 863–868
DOI 10.1002/art.27289
© 2010, American College of Rheumatology

The Protective Effect of Antimalarial Drugs on Thrombovascular Events in Systemic Lupus Erythematosus

Arthritis & Rheum 2010; 62:863-8

Recent reports are controversial regarding the effects of smoking on antimalarial efficacy

ORIGINAL ARTICLE

Clinical and Pharmacogenetic Influences on Response to Hydroxychloroquine in Discoid Lupus Erythematosus: A Retrospective Cohort Study

Shyamal Wahie¹, Ann K. Daly¹, Heather J. Cordell², Mark J. Goodfield³, Stephen K. Jones⁴, Christopher R. Lovell⁵, Andrew J. Carmichael⁶, Mary M. Carr⁷, Angela Drummond⁸, Sivakumar Natarajan⁹, Catherine H. Smith¹⁰, Nick J. Reynolds^{1,11} and Simon J. Meggitt^{1,11}

J Invest Dermatol. 2011 Oct;131(10):1981-6

STUDY

Impact of Smoking in Cutaneous Lupus Erythematosus

Evan W. Piette, MD; Kristen P. Foering, MD; Aileen Y. Chang, BA; Joyce Okawa, RN; Thomas R. Ten Have, PhD, MPH†; Rui Feng, PhD; Victoria P. Werth, MD

Arch Dermatol. 2012 Mar;148(3):317-22.

Increased risk of cancer among 3663 patients with cutaneous lupus erythematosus: a Swedish nationwide cohort study

- Case-control study from Sweden, investigators matched 3,663 CLE patients with 10,989 controls of similar age, sex, and location of residence
- 183 cancers among the CLE patients (HR = 1.8)
- Most frequent cancers were NMSC, buccal cancer, non-Hodgkin lymphoma, and “respiratory” cancer
- Limitations: Many patients with CLE diagnosed by PCPs; co-morbid factors not captured including as smoking, sunbathing habits, immunosuppressive treatment, alcohol intake, body-mass index, or hormonal therapy
- Bottom line: cancer screening might be reasonable, but this is another reason for patients with LE not to smoke

Antimalarial Therapy – Toxicity

- **Hematologic**
 - Aplastic anemia or agranulocytosis are late events and are rare
 - Hemolysis is more common with G6PD deficiency, but generally not at doses used for dermatologic disease
 - Leukopenia and thrombocytopenia are unusual
- **Gastrointestinal – nausea, diarrhea**

Antimalarial Therapy – Rare Systemic Toxicities

- **CNS – sleep disturbance, paresthesia, headache, confusion, seizures, psychosis**
- **Cardiac – T wave depression, hypotension, cardiomyopathy**
- **Myopathy, elevated muscle-derived enzymes (Kalajian & Callen noted elevations of CK or aldolase in 19% of patients tested, but no correlation with muscle symptoms was noted)***
- **ENT – Hearing loss, tinnitus**

* Arch Dermatol 2009; 145: 597-600

Antimalarial Therapy – Toxicity

- **Blurred vision – disturbance of accommodation (reversible)**
- **Corneal deposits – blurred vision, halos, photophobia (Reversible)**
- **Retinopathy – May be dose related, may progress and rarely reverts**
 - **Chloroquine > hydroxychloroquine >>>> quinacrine**

Antimalarial Therapy – Cutaneous Toxicity

- **Pigmentation of the skin – blue-black or brown deposition. Often reversible (slowly).**
- **Yellow-orange with quinacrine**
- **Drug eruption seems to be more common in patients with dermatomyositis***
- **Exacerbation of psoriasis?**
- **Bleaching of the hair**

*Pelle & Callen, Arch Dermatol 2002;138:1231-3

Antimalarials – Is there an increased risk of cutaneous drug reactions in patients with dermatomyositis?

- **Case-control study of 68 patients with DM (8 possible ADM)**
 - 42 had taken hydroxychloroquine and all but 3 children were age, sex and race matched with a patient with cutaneous LE who had taken this drug
 - 12/39 v. 1/39 had a drug reaction (1/3 of JDMS) ($p = 0.0032$)
 - 11 reactions were morbilliform, 1 was Stevens-Johnson like syndrome
 - All began within 3 weeks of therapy and were often intensely pruritic.

Antimalarials – Is there an increased risk of cutaneous drug reactions?

- Treatment - discontinuation of the drug and corticosteroids
- Chloroquine therapy was used in 3 patients – 1 developed a morbilliform eruption
- *Conclusions: Antimalarials are associated with a high frequency of non-life-threatening drug eruptions. There may be cross-reactivity between hydroxychloroquine and chloroquine.*

*Pelle & Callen, Arch Dermatol 2002;138:1231-3

Antimalarial Therapy – Monitoring Guidelines

- **Baseline – CBC, CMP, eye examination**
- **Every 6-12 months – repeat baseline testing.**

Screening for Antimalarial Retinopathy

- PDR suggests that screening be conducted on a semiannual basis
- AAO reviewed the risks and notes that for Hydroxychloroquine at doses < 6.5 mg/kg/d or Chloroquine < 3.0 mg/kg/d over a less than 5 years there is minimal risk
- Ophthalmologic examination is recommended for individuals between 40 and 64 years of age every 2-4 years.
- Risk factors that warrant annual examinations:
 - Higher daily dosage
 - Long-term use
 - Obesity (dose should be adjusted)
 - Hepatic or renal dysfunction

Ophthalmology 2002; 109: 1377-82

American Academy of Ophthalmology Update

Revised Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy

Michael F. Marmor, MD,¹ Ulrich Kellner, MD,² Timothy Y. Y. Lai, MD,³ Jonathan S. Lyons, MD,⁴
William F. Mieler, MD,⁵ for the American Academy of Ophthalmology

- Baseline exam when starting
- Begin annual screening 5 years later
- Very low risk, increases with cumulative dose
 - <1-7/1000 users
 - 1% after 5-7 years, higher after 15-20 years

Ophthalmology. 2011. 118(2):415-22.

Methotrexate

- **Folate antagonist – inhibits dihydrofolate reductase which is involved de novo purine synthesis**
- **Indications:**
 - **Approved: Psoriasis, rheumatoid arthritis, cancer**
 - **Other uses: dermatomyositis, sarcoidosis, vasculitis, CTCL and related conditions, bullous dermatoses, neutrophilic dermatoses, chronic eczemas**

Methotrexate for Cutaneous LE

- **43 patients with cutaneous LE**
 - SCLE 16, localized DLE 6, widespread DLE 4, tumid LE 3, chilblain LE 4, LEP 1
 - 7 had systemic LE with cutaneous manifestations
- **Previous therapies – antimalarials 31, azathioprine 6, mycophenolate mofetil 4, and dapsone 2. No previous therapy – 6**
- **Concomitant therapies - antimalarial agents (14), antimalarial agents plus low-dose prednisone (5), and low-dose prednisone (13).**

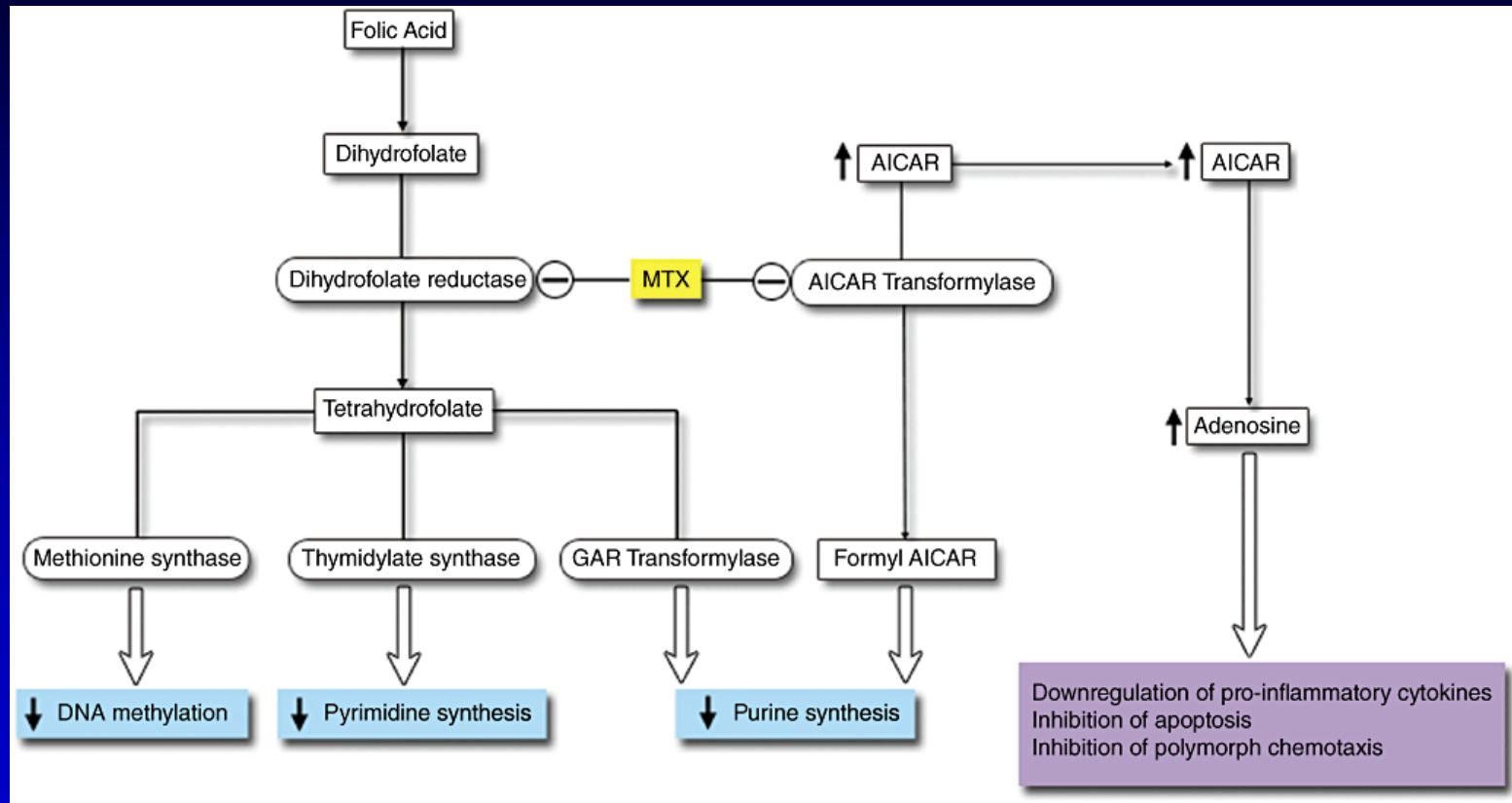
Methotrexate for Cutaneous LE

- **Methotrexate dosage - 15-25 mg/w iv.**
- **Oral folic acid 5 mg was given on the morning following the methotrexate administration.**
- **98% demonstrated marked improvement with minimal toxicity**
- **Lymphopenia was reversed by MTX.**

Methotrexate – Mechanism of Action

- **Anti-proliferative v. immunomodulatory?**
- **Jeffes et al demonstrated that there was a differential sensitivity of lymphoid and epithelial cells to the cytotoxic and growth-inhibitory effects of MTX. (JID 1995; 104: 183-8)**

Methotrexate - Mechanism of Action



Shen et al. *Australasian J Dermatol* 2011; 53: 1-18

Methotrexate - Administration

- Oral, intravenous, intramuscular, intrathecal, subcutaneous
- Pregnancy category - X
- Excretion via the kidneys
- Single weekly dosing or weekly dose split and given q12h x 3
- Daily dosing may be helpful in PRP
- Initial dose – some use a test dose of 2.5 mg
- Cost = \$0.50 per 2.5 mg tablet, \$8.50 25 mg solution

Methotrexate – Administration (Continued)

- **Dosage**
 - 7.5 to 25 mg/week for psoriasis
 - 25-50 mg/week for collagen-vascular diseases
- **Addition of folic acid 1 mg bid will lessen GI intolerance, frequency and severity of oral ulceration, but may compromise the effectiveness**

Methotrexate - Toxicity

- **Hematologic-correlates with renal function**
- **Hepatic-increased in obesity, alcoholics, diabetes**
- **Gastrointestinal-nausea, vomiting, diarrhea**
- **Pulmonary-rare in dermatologic patients**
- **Reproductive-azospermia, effects on fetus**
- **Malignancy risk-only in selected subsets**

Methotrexate – Hematologic Toxicity

- **Presence of renal insufficiency**
- **Older patient**
- **Concomitant administration of trimethoprim containing compounds**
- **May be preceded by an increasing MCV**
- **Leucovorin rescue might be helpful**

Methotrexate - Hepatotoxicity

- **Increased risk**
 - **Alcoholism**
 - **Obesity**
 - **Diabetes mellitus**
 - **Elderly patient**
- **Patients should be pretested for Hepatitis C**
- **Liver biopsy is recommended by AAD guidelines at every 1-1.5 gm cumulative dosage for psoriatics**

Aithal et al studied 122 liver biopsies in 66 psoriasis patients

- **Mean cumulative dose – 3206 mg over 280.5 weeks**
- **2 pre-treatment biopsies demonstrated advanced cirrhosis, both patients were heavy drinkers**
- **Probability of advanced cirrhosis**

Dose	1500	3000	4500	5000	6500
%	0%	2.6%	2.6%	8.2%	8.2%

- **Incidence is low and liver biopsy has little impact on therapy**

Ailment Pharmacol Ther 2004; 19: 391-9

Methotrexate and liver fibrosis

- **Study of 71 patients with 169 liver biopsies**
- **71% developed fibrosis (96% with risk factors v. 58% without)**
- **Severe fibrosis developed in 38% v. 9%**
- **Cirrhosis developed in 3 patients (all with one or more risk factor) and in 2 patients with normal liver histology at onset of therapy it developed at 10 and 17 years**

Methotrexate and liver fibrosis

- **Risk factors**
 - **Excessive alcohol consumption (>30 gm/d) – 9/9 v. 41/62**
 - **Type 2 DM – 7/7 v. 37/64**
 - **BMI > 25 – 14/15 (5/14 had severe fibrosis)**
- **An accompanying editorial discusses the mechanism of liver injury including host (genetic) factors and environmental factors**

Comment – methotrexate and liver fibrosis

- 1. It remains necessary to perform periodic liver biopsies in patients on MTX**
- 2. Perhaps polymorphisms of the MTHFR gene (677C to T) might predispose an individual to MTX injury (accompanied by mild hyperhomocysteinemia)**
- 3. Concomitant use of folic acid might decrease the frequency or severity of liver fibrosis**
- 4. TNF antagonists might improve liver outcome**

J Hepatol 2007; 46: 995-8 and 1111-8

Role of LFTs in Detecting Liver Damage in Sarcoidosis

- **100 liver biopsies in 68 patients with sarcoidosis**
- **Identified 4 groups**
 - **Sarcoidosis (47), toxic reaction to MTX (14), hepatitis C (2), normal liver tissue (37)**
- **Among the 14 patients with toxicity due to MTX there were 5 with previously normal biopsies**
- **Serial LFTs were not useful in predicting toxicity**

Arch Intern Med 2003; 163: 615-20

Liver Disease and Methotrexate

- **Liver biopsy is not without complications**
- **There is a debate about the nature of the cirrhosis that might complicate methotrexate therapy**
 - **Improvement occurs with cessation**
 - **Continued therapy may not worsen the liver**
 - **Un-monitored patients may require liver transplantation**

Risk of neoplasia - Methotrexate

- **Not present in psoriatic patients**
- **Lymphomas, primarily B-cell, have been reported in patients with collagen vascular disorders**
- **Some of the lymphomas are reversible following cessation of the methotrexate**

» NEJM 1993; 328: 1317-9

**Methotrexate-associated B-cell
Lymphoproliferative
Disorders Presenting in the Skin:
A Clinicopathologic and
Immunophenotypical Study of 10 Cases**

**Koens L et al. Am J Surg Pathol.
2014 May 6.
Netherlands**

Objective

- **To determine if MTX-associated B-LPDs show characteristic clinicopathologic features that allow their recognition, even in the absence of adequate clinical data, and may be used in the differentiation from other cutaneous B-cell lymphomas**

Results

- **Diseases: RA, psoriatic arthritis, dermatomyositis, Still disease.**
- **5 EBV + cases and 5 EBV – cases**
- **Median age was 76 years**
- **Median time of MTX treatment was 4 years**
- **Extracutaneous disease in 4/10 patients**
- **Complete resolution with MTX withdrawal in 4 cases (2 EBV + and 2 EBV -)**
- **Median f/u 24 mos, only 1 died of lymphoma.**

Methotrexate - Drug Interactions

- **Trimethoprim**
- **NSAIDs, particularly indomethacin may worsen renal function. Also, they may displace MTX from protein.**
- **Phenytoin-levels increase with MTX**
- **Radiation or photo-recall**

Monitoring Methotrexate Therapy

- **Baseline:**
 - **CBC, comprehensive metabolic panel, Hepatitis panel (specifically Hep C Ab)**
 - **Assess risk factors – alcohol, HIV, renal fxn**
 - **Liver biopsy in high risk patients**

Monitoring Methotrexate Therapy -Follow-up

- **CBC, Hepatic function panel – q2w x2 then q3mos.; or with dose escalation**
- **For Psoriasis patients – Current Guidelines suggest that liver biopsy be performed every 1-1.5 gm total dose, sooner if hepatic function is abnormal**
- **Unknown value in patients with other diseases, except for sarcoidosis in which liver biopsy seems prudent**
- **Future role for amino-terminal propeptide of type III procollagen? (not available in the US)**

Is a test dose needed?

- **Suggested for those “at risk” patients.**
- **Risk factors for hematologic toxicity**
 - Renal insufficiency**
 - Elderly**
 - Folate deficiency (high baseline MCV)**
 - Concomitant drugs that decrease MTX clearance**
 - Hypoalbuminemia**
 - Greater than moderate alcohol intake**

Folic Acid necessary?

- **Decreases GI, Heme, and Liver adverse effects *without compromising efficacy****
- **Decreases serum homocysteine levels**
- **Daily dosing even on MTX day**
- **Both folic acid and folinic acid (leucovorin) are comparable for reducing MTX toxicity**

*Strober, Menon. *JAAD* 2005; 53(4):652.
Prey and Paul. *Br J Dermatol* 2009;160:622.
Van Ede et al. *Arthritis Rheum* 2001;44:1515.

How much Folic Acid?

- **Increasing dose FA dose may help s.e**
- **2 new studies suggest ↓ efficacy w/ FA**
- **No head-to-head trial comparing 1 vs 5mg**
- **Epi studies inverse assoc b/t folate status and cancers (prostate, colorectal) and cardiovascular risk but meta-anaylsis unclear.**

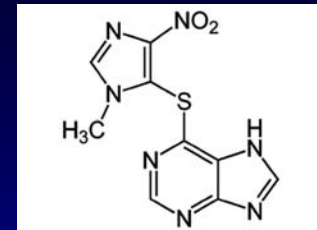
Chladek et al. *Eur J Clin Pharmacol* 2008;64:347.

Salim et al. *Br J Derm* 2006;154:1169.

Huang et al. *Clin Nutr* 2012;31(4)448-454.

<http://ods.od.nih.gov/factsheets/Folate>

Azathioprine



- Purine analog
- Competitive inhibition of purine metabolism leading to effects on DNA & RNA formation
- *In vivo* converted to 6-mercaptopurine (Purinethol)
- Affects cell mediated immunity more than humoral immune function

Azathioprine - Indications

- **Approved:**
 - Transplantation
 - Rheumatoid arthritis
- **Off-label uses**
 - Immunobullous diseases
 - Collagen vascular disorders
 - Neutrophilic dermatoses – Sweet's, PG
 - Eczemas

Azathioprine – Uses in Dermatology*

- Chronic actinic dermatitis
- Aphthous stomatitis
- Atopic dermatitis
- Behcet's disease
- Bullous pemphigoid
- Dermatomyositis
- Nummular eczema
- Eosinophilic fasciitis
- EBA
- Hydroa vacciniforme
- Cutaneous lupus erythematosus
- Weber-Christian disease
- Leprosy reactions
- Leukocytoclastic vasculitis
- Lichen planus
- Mucous membrane pemphigoid
- Pemphigus
- Pityriasis rubra pilaris
- PMLE
- Prurigo nodularis
- Psoriasis
- Pyoderma gangrenosum
- Relapsing polychondritis
- Sarcoidosis

*All are "off-label uses

Lebwohl et al: Treatment of Skin Diseases 3rd edition 2009

Azathioprine

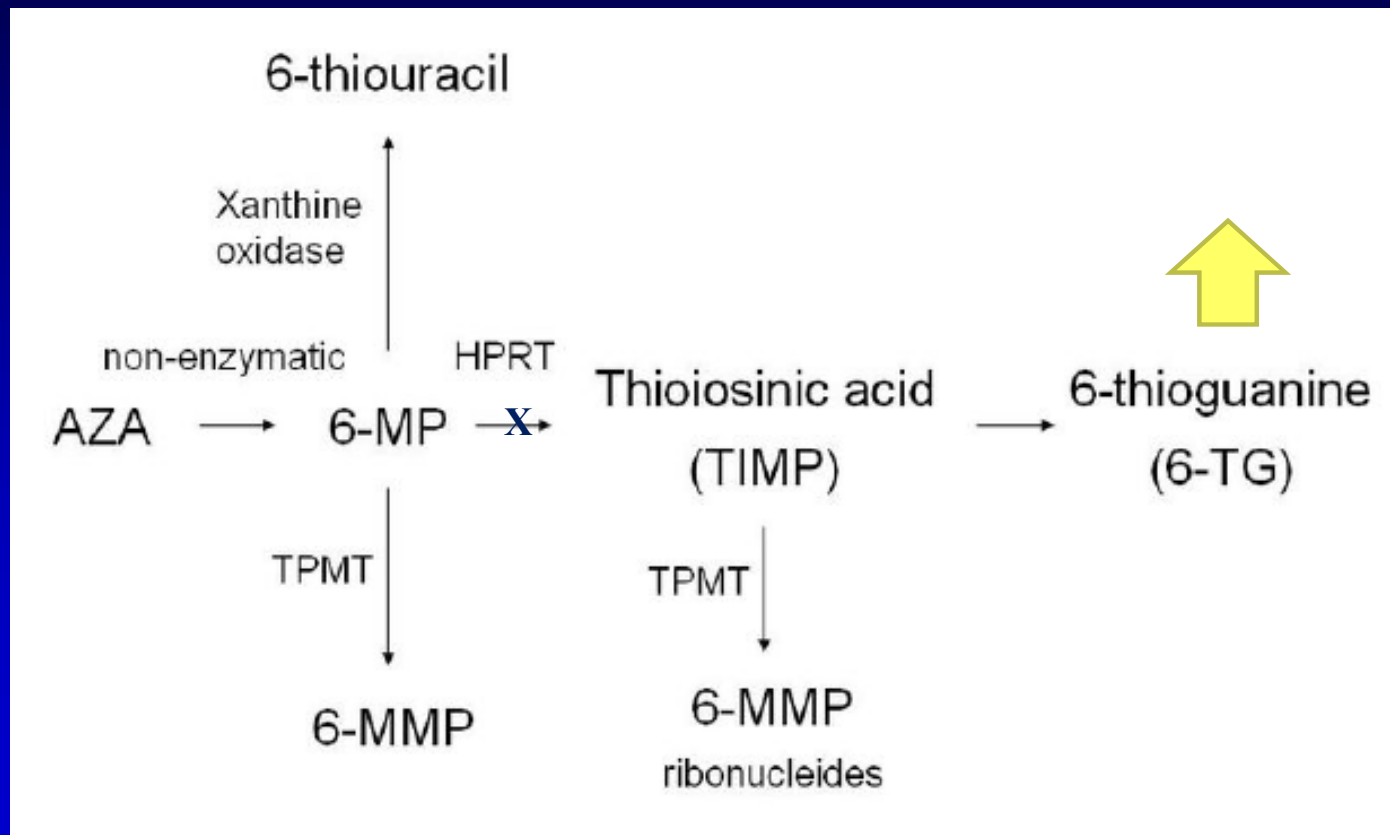
- **Formulation – 50 mg scored tablets**
- **Cost = \$1.10/50 mg tablet**
- **Dosage – 2 mg/kg/d**
- **Pregnancy category - D**
- **Reduce dose in patients low levels (homozygous deficiency) of thiopurine methyltransferase (TPMT)**
- **Consider increased dose in patients with high levels of TPMT**
- **Expect therapy to demonstrate effectiveness between 6 & 8 weeks**



Azathioprine

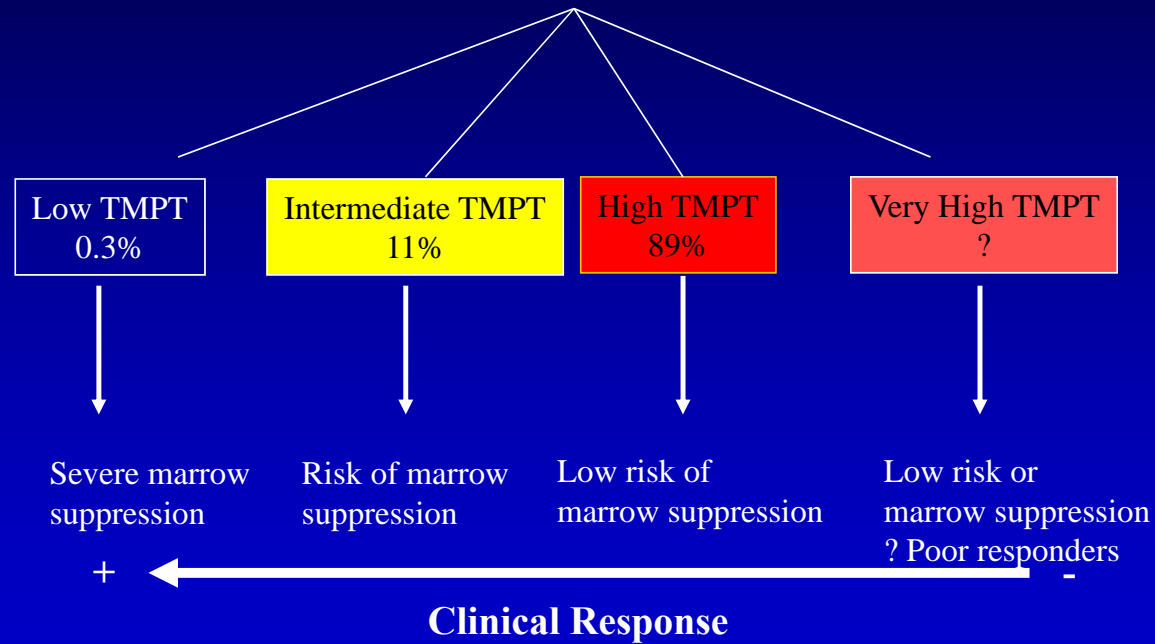
Enzymatic Pathway	End Products	What inhibits Enzyme
TMPT	Inactive metabolites	Genetic polymorphisms
XO	Inactive metabolites	Allopurinol
HGPRT	Active purine analogs (sp. 6-thioguanine)	Lesch-Nyhan syndrome

Toxicity due to absence of TMPT



Thiopurine methyl transferase

Allelic Polymorphism



AZA – Adverse Reactions

- **Early (< 1 month)**
 - **Pancytopenia – enhanced in persons deficient in TPMT**
 - **Hypersensitivity syndrome***
 - **Fever, rash, cardiovascular collapse, hepatitis, pancreatitis, pulmonary compromise, renal insufficiency, nausea**
- **Late, dose & duration-dependent**
 - **Increased risk of infections – viral, fungal, opportunistic**
 - **Increased risk of neoplasia**

*Inositol triphosphate pyrophosphatase polymorphisms may be associated with early adverse reactions

AZA - Drug Interactions

- **Allopurinol and febuxostat – decrease dose of AZA by 75% - increased risk of pancytopenia**
- **ACE inhibitors may increase risk of leukopenia**
- **Warfarin – AZA may decrease INR**
- **Other immunosuppressive agents – increased risk of cytopenia and infection**
- **Mesalamine – also affects TMPT activity and enhances immune suppression**
- **Echinacea – may decrease immunosuppression**
- **Vaccinations – no live vaccines, attenuated response to other vaccines may occur**

Azathioprine – Monitoring Guidelines

- **Baseline – CBC, CMP, TPMT, ? PPD**
- **Follow-up:**
 - **CBC, Hepatic function panel – every 1-2 weeks and during dosage escalation**
 - **CBC, Hepatic function panel ever 2-3 months**
 - **Consider measuring 6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP) levels to monitor therapy**
- **Caution! Reduce dosage dramatically in the presence of allopurinol and febuxostat**

Mycophenolate Mofetil

- **Administration – oral - 250 or 500 mg tablets or suspension 200 mg/ml**
- **Dosage - 500 to 1500 mg bid**
- **Cost = \$6.90 per 500 mg tablet (\$900 – 1200/mo), Suspension cost is between \$700 and 2400/mo**
- **Time to response ~ 12 weeks**
- **Pregnancy category – D**
- **Risk Evaluation and Mitigation Strategy (REMS) approved September 2012**



MYCOPHENOLATE REMS

RISKS OF FIRST TRIMESTER PREGNANCY LOSS AND CONGENITAL MALFORMATIONS



Prescribers

To enroll or order materials
[click here](#)



Pharmacists

For Pharmacists Overview
[click here](#)



Patients

For Patient Overview
[click here](#)

<https://www.mycophenolaterems.com/Default.aspx>

MMF: Mechanism of Action

- **MMF is rapidly absorbed and converted to MPA**
- **MPA is rapidly converted to its inactive glucuronide in the liver**
- **Tissues with β -glucuronidase convert inactive MPA glucuronide to its active form**
- **MPA acts as a noncompetitive inhibitor of inosine monophosphate dehydrogenase**

Mycophenolate Mofetil - Indications

- **Approved:**
 - **Transplantation**
- **Off-label uses:**
 - **Immunobullous diseases**
 - **Collagen-vascular diseases**
 - **Eczemas**
 - **Lichen planus**
 - **Psoriasis**
 - **Pyoderma gangrenosum**
 - **Vasculitis**

MMF for SCLÉ resistant to standard therapy

- **Prospective, non-randomized pilot study of 10 patients with SCLÉ (4 PS, 6 A) using the CLASI**
- **Prior therapies – antimalarials (10), SS (7), azathioprine (3)**
- **1440 mg/d of enteric-coated MMF for 3-months**
- **7/10 were heavy smokers**

Br J Dermatol 2007; 156: 1321-7

Mycophenolate Mofetil for Myositis

Study	Design	No. of patients Rx/dose	Response	Toxicity
Gelber et al (2000)	Open label	4 with refractory DM/1 gm b.i.d	Cs sparing	None noted
Majithia (2004)	Open label	4 DM/3PM	“Good” response skin and muscles	
Rowin et al (2006)	Open label	10 DM/1 gm b.i.d.	6/10 responded	3 opportunistic infections (1 death)
Edge et al (2006)	Open label	12 DM/500-1500 mg b.i.d.	10/12 responded	1 CNS lymphoma, 1 hepatitis, 1 urinary sx
Rouster-Stevens et al (2010)	Retrospective analysis	50 JDMS/20 mg/kg/d	Measurable response of myopathy and skin and Cs sparing	None noted
Dagher et al (2012)	Open label	8 JDMS/800 to 1,350 mg/m ² /day	Objective muscle response and Cs sparing	Transient neutropenia in 1 pt

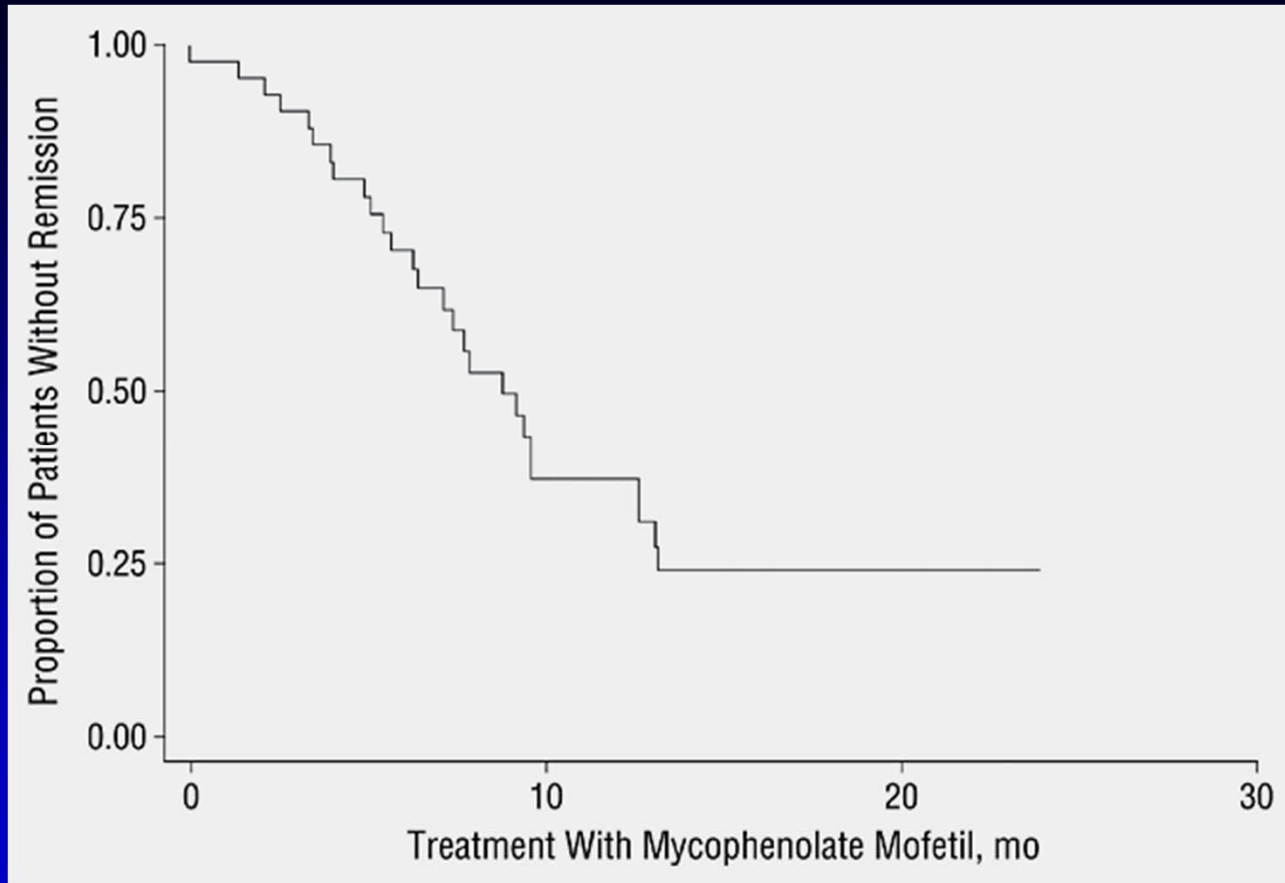
Mycophenolate Mofetil for DM/ILD

Study	Design	No. of patients Rx/dose	Response	Toxicity
Morganroth et al (2010)	Open label	4 with refractory DM/1 gm b.i.d	¾ normalized their PFTs including DLCO	None noted
Mira-Avendano IC (2013)	Retrospective analysis	9 DM or PM/Mean dose 2.2 gm/d	CS sparing (no difference between Cyclophosphamide and azathioprine)	Mild toxicity in 4 patients - NOS

MMF for PV and PF

- **42 consecutive patients with PV (31) or PF (11)**
- **35-45 mg/kg/day (70 kg person = 2 gm/d)**
- **Evaluated for remission as well as the ability to taper or stop concomitant therapies**
- **Remission was achieved in 22/31 PV patients and 5/11 PF patients varying between 1-13 months (mean 9 months)**
- **Toxicity – mild gastrointestinal distress**

Treatment of pemphigus vulgaris and pemphigus foliaceus with mycophenolate. Arch Dermatol 2003; 139: 739-42.



Mimouni, D. et al. Arch Dermatol
2003;139:739-742.

MMF - Atopic Dermatitis

- Arch Dermatol 2001; 137: 870-3
 - Open-label pilot study of 10 patients with non-responsive AD (9 treated with Prednisone, 2 with PUVA, 2 with UVA/B and 2 with CyA)
 - 1 gm b.i.d. for 4 weeks then 500 mg b.i.d.
 - Improvement in all patients at 4 weeks, sustained improvement in 6/7 patients at 20 weeks
 - One patient had to d/c secondary to HSV retinitis
- Br J Dermatol 2007; 157: 127-31
 - Open label study of 14 patients (2-16 y/o) with severe AD treated with MMF 30-50 mg/kg/d as a sole systemic therapy
 - CR – 4, > 90% (ACR) – 4, 60-90% - 5, failure – 1
- J Drugs Dermatol. 2010;9:356-62.
 - Open label study of 16 patients.
 - 14/16 improved (3CR, 6 near CR)

MMF: Adverse Effects

- **GI: nausea, vomiting, diarrhea, abdominal cramps**
- **GU: urgency, dysuria, frequency, sterile pyuria**
- **ID: increased risk of infections**
 - **Progressive multifocal leukoencephalopathy**
- **Malignancy: lymphoma, ?NMSC**

MMF – Drug Interactions

- **Immunosuppressants – increased infection and neoplasia**
- **Antacids – lower absorption**
- **Acyclovir, ganciclovir – compete for excretion in patients with renal insufficiency**
- **Antibiotics may alter GI flora and impair enterohepatic circulation**

Mycophenolate Mofetil

- **Prior to therapy – CBC, CMP seem reasonable, but there are no specific monitoring guidelines. Provide a handout written in lay language about MMF (e.g. USP DI patient handout)**
- **While on Therapy – although there are no specific guidelines, periodic CBC and CMP seem reasonable**

Conclusions

- **These drugs can be used safely in motivated, intelligent patients**
- **Utilize handout material from companies or from foundations or societies**
- **Discuss R, B & A with your patient**
- **Follow guidelines that exist or discuss deviations with the patient**
- **Document, document, document!!!**