Updates in Management of Idiopathic Inflammatory Myopathies

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دانشگاه علوم پزشکی مشهد
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Disclaimer

- Noting to disclose

Case Presentation

- 16 year-old female
- Progressive weakness since three months prior to referral
- 3/5 proximal weakness in lower limbs, mild proximal weakness in arms
- Systemic exam: Nl
- CK: 6400 to 9700
- EMG: Irritable myopathic process
- Echo and Chest HRCT: Nl
- Lab work: Nl/Neg except for positive Anti-HMGCoA Reductase Ab
- Muscle biopsy: Necrotizing myopathy

Clinical Data : Proximal and axial muscle weakness since 3 months ago. CK=6399. EMG=Irritable myopathic. Parents are not relative.

Mac:
Muscle biopsy obtained by open technique and frozen in isopentane cooled in liquid nitrogen. One frozen and one paraffin block were prepared.

Mic:

- H&E stain reveals striated muscle tissue with variation in fiber size. Multiple necrotic and degenerative/regenerative fibers are seen dispersed in the fascicles with myophagocytosis. Internalized nuclei are seen. Multiple whorled fibers are seen. Atrophic fibers are round or angular and dispersed. Freeze artefact is seen.
  Endomysial connective tissue seems normal. No inflammation. No adipose tissue replacement. Partial invasion is also seen.
- Gomori trichrome stain reveals no ragged red fiber. Rare red rimmed vacuoles are seen.
- Congo red stain reveals no congophilic inclusion.
- ORO stain reveals fine lipid droplets in muscle fibers.
- PAS stain reveals some fibers containing granular PAS-positive materials digested by diastasis.
- NADH-TR reaction reveals good differentiation of muscle fibers. Multiple small dark angular fibers are seen. Multiple whorled fibers are noted.
- SDH reaction reveals no prominent abnormal mitochondrial proliferation.
- Cox reaction reveals multiple whorled fibers.
- Cox+SDH reaction reveals no cox-negative fiber.
- ATPase reactions PH 9.4, 4.63 and 4.35 reveal slight type 1 fibers predominance. No fiber type grouping. Most of the atrophic angular fibers are type 2. Fibers type 2C are seen.
- MHC1: Expression on sarcolemma of almost all fibers with strong expression on necrotic and degenerative/regenerative fibers as well as endomysial expression.

DX: Left deltoid, muscle biopsy:

- Myopathic atrophy with multiple necrotic and degenerative/regenerative fibers but no inflammation associated with multiple whorled fibers.

What is the best Tx plan for this patient with necrotizing myopathy?

1. High dose CS
2. Monthly IVIG
3. Triple therapy: High dose CS + IVIG + MTX
4. Rituximab

Are there reliable/enough clinical trials?

- Paucity of prospective, double-blinded, placebo-controlled trials
- Many retrospective and unblinded and lacked placebo control trials
- Many case reports
- In several reports, patients with subjective improvement or lower serum CK levels were defined as positive responses rather than objective improvement

Journal: *Expert Opinion on Emerging Drugs*

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Clinical trials and novel therapeutics in Dermatomyositis

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Abstract

Introduction: Currently, there are no proven drugs that are FDA approved for the treatment of dermatomyositis (DM), even though multiple clinical trials are ongoing to evaluate safety and efficacy of novel therapeutics in DM. The purpose of this review is to highlight the biological plausibility, existing clinical evidence as well as completed and ongoing clinical trials for various drugs in pipeline for development for use in dermatomyositis.

Cochrane Library

Cochrane Database of Systematic Reviews

Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis (Review)

Gordon PA, Winer JB, Hoogendijk JE, Choy EHS

Therapy	Route	Dose	Side Effects	Monitor
Prednisone	Oral	0.75–1.5 mg kg per day to start	Hypertension, fluid and weight gain, hyperglycemia, hypokalemia, cataracts, gastric irritation, osteoporosis, infection, aseptic femoral necrosis	Weight, blood pressure, serum glucose/potassium, cataract formation
Methylprednisolone	Intravenous	1 g in 100 mL/normal saline over 1–2 hours, daily or every other day for 3–6 doses	Arrhythmia, flushing, dysgeusia, anxiety, insomnia, fluid and weight gain, hyperglycemia, hypokalemia, infection	Heart rate, blood pressure, serum glucose/potassium
Azathioprine	Oral	2–3 mg/kg per day; single a.m. dose	Flu-like illness, hepatotoxicity, pancreatitis, leukopenia, macrocytosis, neoplasia, infection, teratogenicity	Blood count, liver enzymes
Methotrexate	Oral	7.5–20 mg weekly, single or divided doses; one day a week dosing	Hepatotoxicity, pulmonary fibrosis, infection, neoplasia, infertility, leukopenia, alopecia, gastric irritation, stomatitis, teratogenicity	Liver enzymes, blood count
	Subcutaneously	20–50 mg weekly; one day a week dosing	Same as oral.	Same as p.o.
Cyclophosphamide	Oral intravenous	1.5–2 mg/kg per day; single a.m. dose 0.5–1.0 g/m^2 per month × 6–12 months	Bone marrow suppression, infertility, hemorrhagic cystitis, alopecia, infections, neoplasia, teratogenicity	Blood count, urinalysis
Cyclosporine	Oral	4–6 mg/kg per day, split into two daily doses	Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsutism, tremor, gum hyperplasia, teratogenicity,	Blood pressure, creatinine/BUN, liver enzymes, cyclosporine levels,
Tacrolimus	Oral	0.1–0.2 mg/kg per day in two divided doses	Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsutism, tremor, gum hyperplasia, teratogenicity,	Blood pressure, creatinine/BUN, liver enzymes, tacrolimus levels
Mycophenolate mofetil	Oral	Adults (1 g BID to 1.5 g BID) Children (600 mg/m^2/dose BID (no more than 1 g per day in patients with renal failure)	Bone marrow suppression, hypertension, tremor, diarrhea, nausea, vomiting, headache, sinusitis, confusion, amblyopia, cough, teratogenicity, infection, neoplasia	Blood count
Intravenous Immunoglobulin	Intravenous	2 g/kg over 2–5 days; then 1 gm/kg every 4–8 weeks as needed	Hypotension, arrhythmia, diaphoresis, flushing, nephrotoxicity, headache, aseptic meningitis, anaphylaxis, stroke	Heart rate, blood pressure, creatinine/BUN
Rituximab	Intravenous	A course is typically 750 mg/m^2 (up to 1 g) and repeated in 2 weeks or 375 mg/m^2 weekly Courses are then repeated usually every 6–18 months	Infusion reactions (as per IVIG), infection, progressive multifocal leukoencephalopathy	Some check B-cell count prior to subsequent courses (but this may not be warranted)

Launching a treatment plan hinges on answers to two critical questions:

1. Is the process life-threatening?
2. Is the process limb-threatening?

If the answers are affirmative to either one, then we are dealing with a case of

“AGGRESSIVE IIM”

Aggressive/severe cases of IIMs

- Evidence suggests that atrophy and fatty replacement of muscle tissue is established early after the onset of disease, and thus, delayed treatment can lead to long-term disability

How can we figure out which myositis is AGGRESSIVE?

1. Acute onset and rapidly progressive weakness
2. Dysphagia
3. Evidence of ILD
4. SRP positive necrotizing myopathy
5. MDA-5 positive DM (with any evidence in favor of ILD)

Management of Severe/aggressive IIMs

- Triple drug therapy:

1. High dose CS with an initial bolus
2. Second line agents (AZT, MTX, MMF)
3. IVIG

- **Rituximab** should be considered in patients with refractory disease

Management of severe/aggressive IIM Dysphagia

- Given the risk of aspiration, patients with inflammatory myopathies with dysphagia other than IBM should receive a **three-drug** regimen that is similar to that given to patients with severe weakness.
- In severe cases with extremely severe dysphagia local therapies such as **cricopharyngeal myotomy**, **pharyngoesophageal balloon dilatation**, and injection of **BTX** into the upper esophageal sphincter have shown a reasonable benefit in improving dysphagia
- Swallowing physical therapy is also helpful

Management of severe/aggressive IIM ILD

- 50–60% of patients with anti-MDA5-positive inflammatory myopathies develop ILD soon after the onset of disease, and >85% will have rapidly progressive forms of the illness
- **30–50%** of patients who develop rapidly progressive ILD will **die** during the first year after the onset of lung disease
- Patients who are positive for **anti-MDA5** autoantibodies, should be intensively treated from disease onset with **glucocorticoids** and a **second-line immunosuppressant** agent (eg, **tacrolimus** or **MMF**)

Management of severe/aggressive IIM ILD

Also

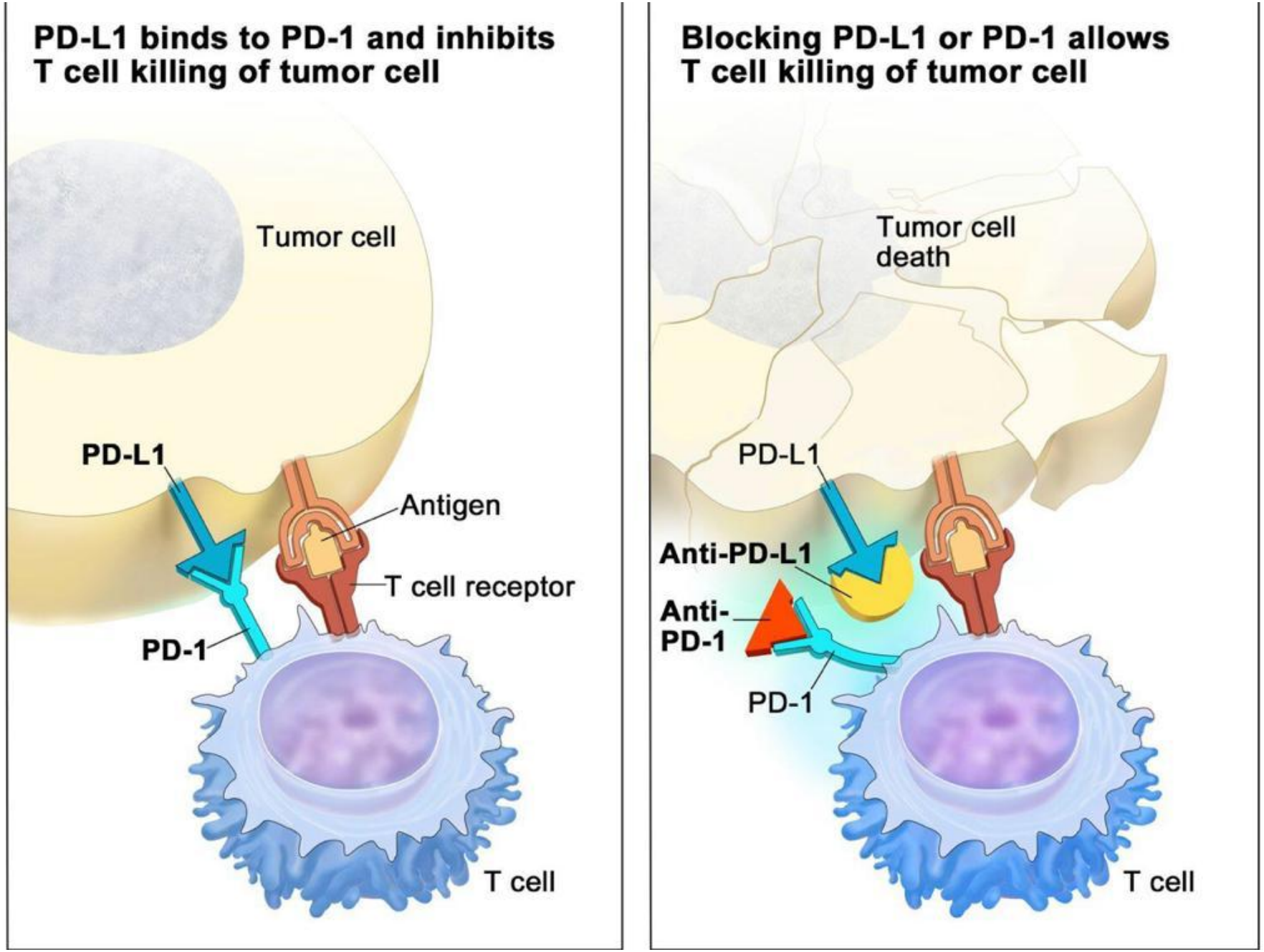
- Daily **plasmapheresis** over the course of 3 days and on alternate days thereafter until the completion of seven sessions
- And 400 mg intravenous immunoglobulin per kg after each plasmapheresis session

Management of severe/aggressive IIM ILD

- Lung transplantation

Management of severe/aggressive IIM
Immune Check point Inhibitor associated IMNM

- Immune checkpoints are a normal part of the immune system.
- Their role is to prevent an immune response from being so strong that it destroys healthy cells in the body.
- When the checkpoint and partner proteins bind together, they send an “off” signal to the T cells. This can prevent the immune system from destroying the cancer.
- Blocking checkpoint proteins from binding with their partner proteins prevents the “off” signal from being sent, allowing the T cells to kill cancer cells.



Immune Check point Inhibitor associated IMNM

- Pembrolizumab (Keytruda)
- Nivolumab (Opdivo)
- Cemiplimab (Libtayo)

Immune Check point Inhibitor associated IMNM

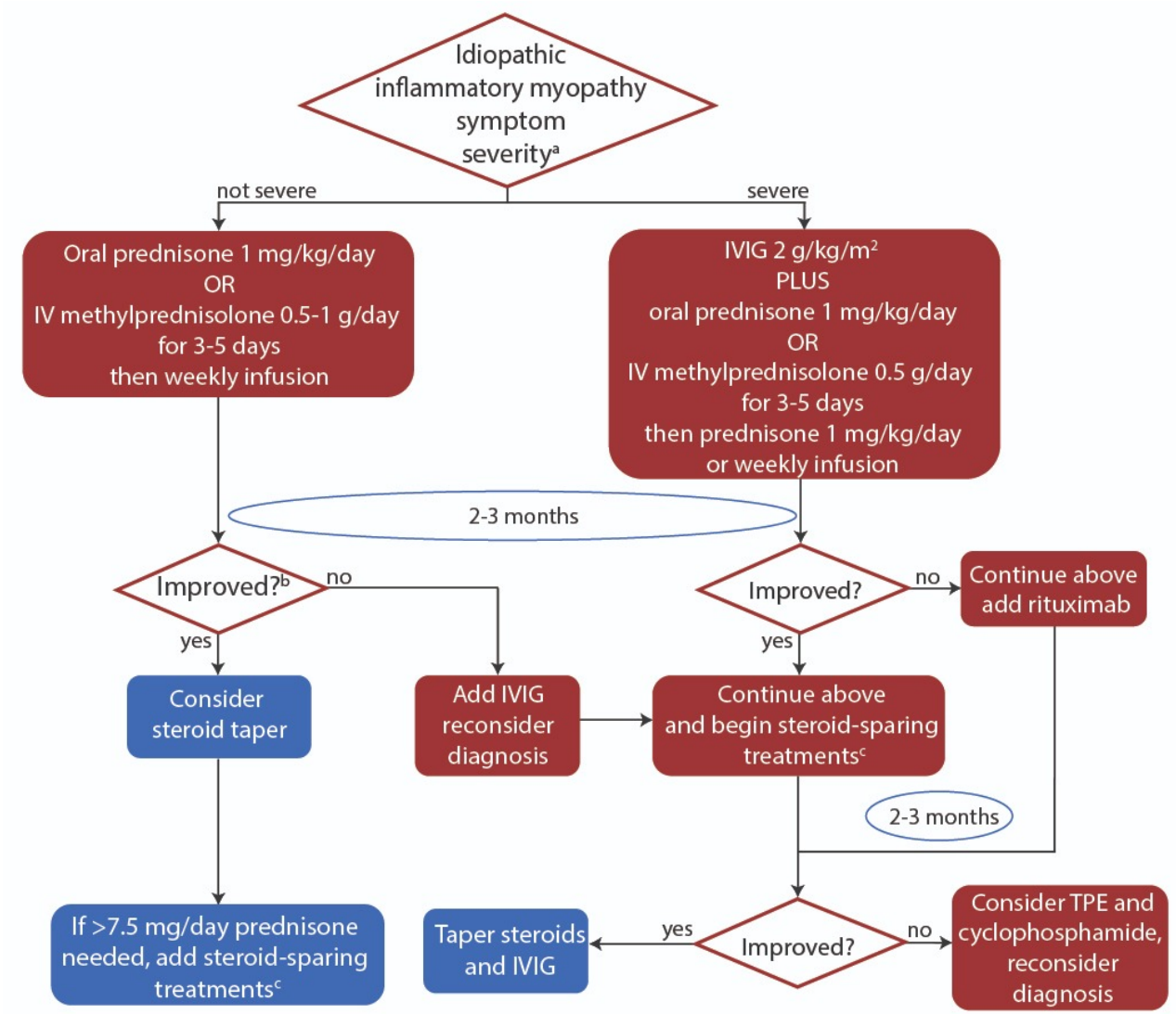
- Melanoma
- Breast cancer
- Kinney cancer
- Lung Cancer
- GI cancer
- HL

Immune Check point Inhibitor associated IMNM

- Thyroiditis
- Hepatitis
- Pneumonitis
- Colitis
- **Myositis**

SLONM

- Sporadic late onset nemalin myopathy



[a] nonambulatory, antiSRP+, or ICI-associated IMNM or antiMDA-5+ ILD may require hospitalization and aggressive immunosuppression
[b] response to treatment must include objective improvement in skin rash, muscle strength and function and not CK level
[c] methotrexate, azathioprine, or mycophenolate mofetil

Corticosteroids

Mechanism of Action of Corticosteroids

- inhibit leukocyte traffic and access to the sites of inflammation
- interfere with production of humoral factors including prostaglandins leukotrienes, and cytokines at the site of inflammation

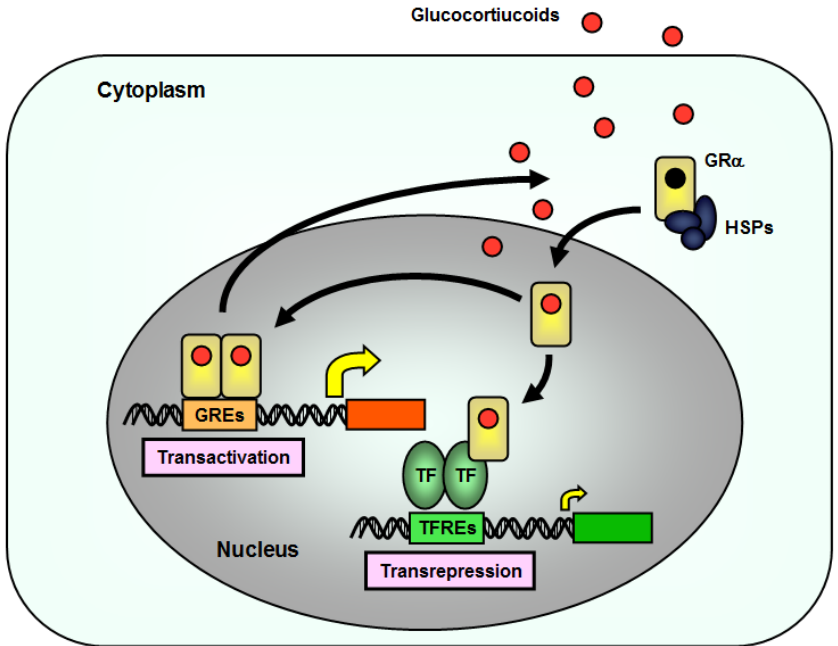
Mechanism of Action of Corticosteroids

1. Genomic effects of CSs
2. Non-genomic effects of CSs

Genomic effects of CSs

- **Transactivation** (upregulation of anti-inflammatory Prs as well as Prs which are contributed in side effects of CSs)
- **Transrepression** (Prevents upregulation of certain genes which are contributed in inflammation)
- Anti- inflammatory and immunosuppressive effects of CSs are mainly mediated by transrepression, while it is thought that many of the side effects of CSs are related to transactivation

GR: GC Receptor
GRE: GC Responsive Element



Non-genomic effects of CSs

- Nonspecific interactions with membrane- bound corticosteroid receptors, nonspecific interactions of corticosteroids with cellular membranes, and non-genomic effects mediated by cytosolic corticosteroid receptors
- These non-genomic effects contribute to the additional **rapid effect** of high-dose corticosteroids
- Dexamethasone and methylprednisolone having **higher non-genomic** effects

Corticosteroids

- No significant improvement in IBM
- One recent large retrospective series reported that IBM patients treated with immunotherapy actually **fared worse** than those who were not treated

Tapering CS

- Tapering by 5 mg per week in daily or alternate daily base
- Alternate day CS is not advised for diabetic patients
- Once the dose is reduced to 10 mg every day or 20 mg every other day, tapering should be slow down as by 2.5–5 mg every 2–4 weeks.

Monitoring response to CS

- 20%-30% of cases response is slow or incomplete
- In those patients who do not respond at all to high-dose prednisone, the clinician needs to consider alternative disorders (e.g., IBM or muscular dystrophy)
- CK level is not essential for adjustment of CS dosage
- But if an increase of CK level happens tapering of CS should slow down or stop (and if clinical deterioration happens dose increase is necessary)

Corticosteroid Myopathy

- Steroid Myopathy should be suspected when there is persistent / increasing weakness, after the serum CK level has declined or normalized
- Usually affects proximal lower limb muscles
- Tx
  - Reduce prednisone dose
  - Alternate day regimen
  - Regular exercise program

Relapse VS steroid myopathy

- Type 2 muscle fiber atrophy
- CK level is Nl
- Other CS side effects
- Lack of irritability on needle EMG

Second Line Therapy

Second Line Therapy

- Are used for:

1. Aggressive/severe cases at the same time of initiation of CS (e.g. necrotizing myositis)
2. For patients with other organ involvement (e.g. ILD and Myocarditis)
3. Patients with poor response to CS (e.g. 2-4 months after starting CS)
4. Relapse during tapering CS
5. As a CS sparing agent

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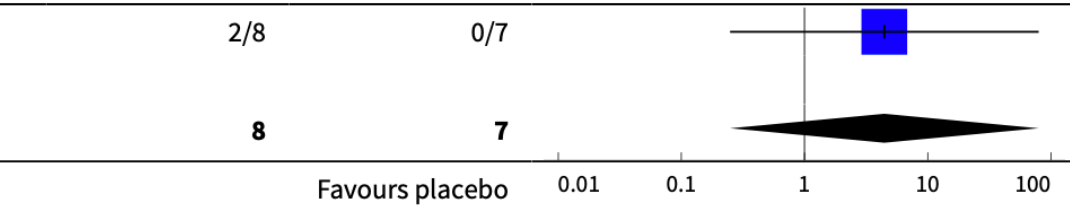
IVIG

IVIG

- Small, uncontrolled studies have reported beneficial response in myositis

Analysis 1.1. Comparison 1 IVIg versus placebo, Outcome 1 Improvement in manual muscle strength by ≧15% at 12 weeks.

Study or subgroup	Favours IVIg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dalakas 1993	2/8	0/7		100%	4.44[0.25,79.42]
Total (95% CI)	**8**	**7**		**100%**	**4.44[0.25,79.42]**



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IVIG

- IVIG seem to be effective in immune-mediated necrotizing myopathy, especially in patients with anti-HMGCR autoantibodies
- Usually used with CS
- Little evidence of effectiveness as monotherapy

IVIG

- Mechanism of action
  - Blockade of Fc receptors
  - Inhibition of complement
  - Direct neutralization of autoantibodies by anti-idiotypes

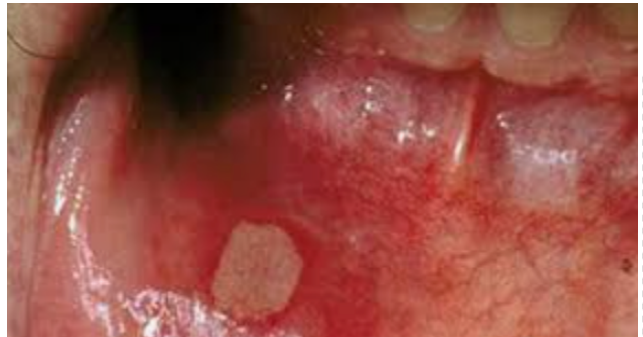
IVIG

- 2 gr/kg over 2-5 days
- Repeat in monthly interval for at least three months
- Then decrease the dose (e.g. 1 gr/kg/month) or spread the dose (e.g. 2 gr/kg/2month)

METHOTREXATE

METHOTREXATE

- Inhibits enzymes responsible for nucleotide synthesis
- No prospective, blinded, controlled studies
- 71-88% effective (retrospective studies)
- Useful in patients with joint symptoms
- Potential lung toxicity (cellcept, tacrolimus and cyclosporine are better choices for patients with ILD)
- Teratogen and oncogene
- Stomatitis, hepatopthy, leukopenia, alopecia



METHOTREXATE

- Once a week
- Starting dose 5 mg/week and the dose is increasing 2.5 mg/week
- Maximum dose 20 mg/week
- If there is no improvement after 1 month of 20 mg per week of oral methotrexate, switch to weekly parenteral (usually sc) methotrexate and increase the dose by 5 mg every week up to 60 mg per week

Follow up lab work for MTX

- Baseline and periodic PFT
- LFT every 2 weeks in beginning and then every 3 months

AZATHIOPRINE

AZATHIOPRINE

- Antagonist of purine metabolism
- AZT is effective in treatment of myositis (retrospective study)
- A prospective, double-blind study comparing azathioprine (2 mg/kg) in combination with prednisone to placebo plus prednisone found **no significant difference** in objective improvement at 3 months
- Better response in CS responsive patients than refractory to CS
- Good choice for CS responsive **predominantly myositis** cases
- A major drawback of azathioprine is that it may take 6–18 months to be effective

AZATHIOPORINE

- Screening for TPMT prior to initiation of AZT
- Initial dose 50 mg/day and increase the dose by 50 mg every two weeks (up to 2-3 mg/kg/day)
- 12% of patients develop systemic reaction like fever, abdominal pain, nausea, vomiting, and anorexia (needs discontinuation)
- Major side effects: bone marrow suppression, hepatic toxicity, pancreatitis, teratogenicity, oncogenicity, and increased risk of infection
- Don’t use with Allouporinol

Follow up lab work for AZT

- CBCs and LFT
- If WBC<4000 the dose should be decrease
- If WBC< 2500 or absolute neutrophile count <1000 AZT is held
- The leukopenia usually reverses within 1 month, and it is possible to then rechallenge without recurrence of the severe leukopenia
- If ALT/AST > 100 AZT is held
- If LFTs return to baseline then rechallenge without recurrence of hepatic dysfunction in some cases

MYCOPHENOLATE MOFETIL

MYCOPHENOLATE MOFETIL (CellCept)

- Blocking purine synthesis in only lymphocytes
- Starting dose 1 gr/day (Bid), can be increased up to 3 gr/day
- Needs adjustment for patients with renal insufficiency (Max 1 gr/day)
- A benefit of MMF compared to other IS agents is the lack of renal or liver toxic
- The most frequent side effect is diarrhea
- Less common side effects include abdominal discomfort, nausea, peripheral edema, fever, and leukopenia
- Good choice for patients with **ILD**

Cyclosporine

Cyclosporine

- Calcineurin inhibitor
- Starting at 3-4 mg/kg/day and then increase to 6
- The cyclosporine dose should initially be titrated to maintain trough serum cyclosporine levels of 50–200 ng/mL
- Blood pressure, electrolytes and renal function should be monitored
- Helpful for DM **skin manifestations** and patient with **ILD**

Tacrolimus

Tacrolimus

- Calcineurin inhibitor
- Started at a dose of 0.1 mg/kg and increased up to 0.2 mg/kg
- Dosing is titrated to maintain a trough level of 5–15 ng/mL
- Blood pressure, electrolytes, and renal function need to be monitored
- Helpful in refractory myositis, DM with severe **skin rashes** and **ILD**

CYCLOPHOSPHAMIDE

CYCLOPHOSPHAMIDE

- There are controversies regarding the efficacy and the toxicity of cyclophosphamide
- Usually reserved for patients who are refractory to prednisone, methotrexate, azathioprine, mycophenolate, IVIG, and rituximab.
- 0.5–1 g IV/m2 per month for 6–12 months
- Can be given orally at a dose of 1.0–2.0 mg/kg per day (with greater risk of hemorrhagic cystitis)
- The major side effects are GI upset, bone marrow toxicity, alopecia, hemorrhagic cystitis, teratogenicity, sterilization, and increased risk of infection and oncogenicity
- Hydration and Mesna

Lab work for Cyclophosphamide

- UA and CBC
- If WBC<4000 the dose should be decrease
- If WBC< 2500 or absolute neutrophile count <1000 Cysclophosphamide is held
- It can be restarted at a lower dose once the leukopenia has resolved
- If hematuria happens it is contraindicated for ever

Biologic Agents

- Rituximab
- Ocrelizumab
- Abatacept
- Tocilizumab

RITUXIMAB

- A large prospective, double-blind, NIH trial found no benefit

ARTHRITIS & RHEUMATISM
Vol. 65, No. 2, February 2013, pp 314–324
DOI 10.1002/art.37754

Rituximab in the Treatment of Refractory Adult and Juvenile Dermatomyositis and Adult Polymyositis

A Randomized, Placebo-Phase Trial

Chester V. Oddis,[1] Ann M. Reed,[2] Rohit Aggarwal,[1] Lisa G. Rider,[3] Dana P. Ascherman,[4] Marc C. Levesque,[1] Richard J. Barohn,[5] Brian M. Feldman,[6] Michael O. Harris-Love,[7] Diane C. Koontz,[1] Noreen Fertig,[1] Stephanie S. Kelley,[1] Sherrie L. Pryber,[8] Frederick W. Miller,[3] Howard E. Rockette,[1] and the RIM Study Group

RITUXIMAB

Objective. **To assess the safety and efficacy of rituximab in a randomized, double-blind, placebo-phase trial in adult and pediatric myositis patients.**

Methods. **Adults with refractory polymyositis (PM) and adults and children with refractory dermatomyositis (DM) were enrolled. Entry criteria included muscle weakness and ≥2 additional abnormal values on core set measures (CSMs) for adults. Juvenile DM patients required ≥3 abnormal CSMs, with or without muscle weakness. Patients were randomized to receive either rituximab early or rituximab late, and glucocorticoid or immunosuppressive therapy was allowed at study entry. The primary end point compared the time to achieve the International Myositis Assessment and Clinical Studies Group preliminary definition of improvement (DOI) between the 2 groups. The secondary end points were the time to achieve ≥20% improvement in muscle strength and the proportions of patients in the early and late rituximab groups achieving the DOI at week 8.**

Results. **Among 200 randomized patients (76 with PM, 76 with DM, and 48 with juvenile DM), 195 showed no difference in the time to achieving the DOI between the rituximab late (n = 102) and rituximab early (n = 93) groups ($P = 0.74$ by log rank test), with a median time to achieving a DOI of 20.2 weeks and 20.0 weeks, respectively. The secondary end points also did not significantly differ between the 2 treatment groups. However, 161 (83%) of the randomized patients met the DOI, and individual CSMs improved in both groups throughout the 44-week trial.**

Conclusion. **Although there were no significant differences in the 2 treatment arms for the primary and secondary end points, 83% of adult and juvenile myositis patients with refractory disease met the DOI. The**

ClinicalTrials.gov identifier: NCT00106184.

RITUXIMAB

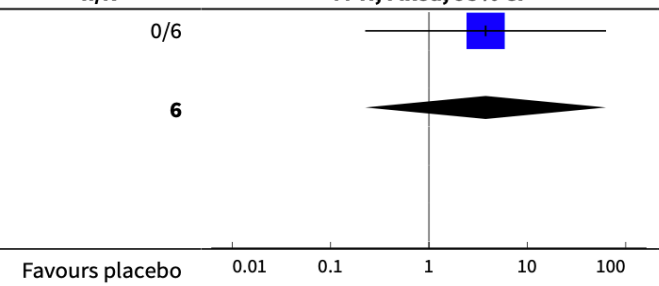
- Post-hoc analysis of the trial and further case series and cohort studies suggested beneficial effects of this drug in patients with antisynthetase syndrome, and in those with anti-Mi2 or anti-SRP autoantibodies
- Rituximab is usually preferred to cyclophosphamide on account of the better tolerance and side-effect profile
- Very small risk of PML

Anti-TNF (Infliximab and Etanercept)

- Conflicting results

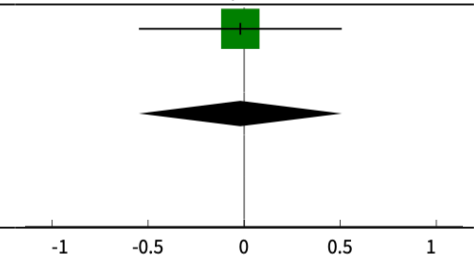
Analysis 4.1. Comparison 4 Infliximab versus placebo, Outcome 1 Improvement in manual muscle strength by ≧15% at 16 weeks.

Study or subgroup	Infliximab n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Coyle 2008	3/12	0/6		100%	3.77[0.23,63.05]
Total (95% CI)	**12**	**6**		**100%**	**3.77[0.23,63.05]**
Total events: 3 (Infliximab), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.92(P=0.36)					



Analysis 7.1. Comparison 7 Etanercept versus placebo, Outcome 1 Mean change in Health Assessment Questionnaire score at 52 weeks.

Study or subgroup	Favours etanercept N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Muscle Study Group 2011	11	-0.3 (0.5)	5	-0.3 (0.5)		100%	-0.02[-0.55,0.51]
Total ***	**11**		**5**			**100%**	**-0.02[-0.55,0.51]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.07(P=0.94)							



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Abatacept

- Is a selective co-stimulation modulator that blocks the activity of T-cells
- In a pilot study with 20 cases Abatacept showed beneficial effects in reducing disease activity and **increasing** the number of regulatory T cells in muscle biopsies of these patients

Other Biologic Agents

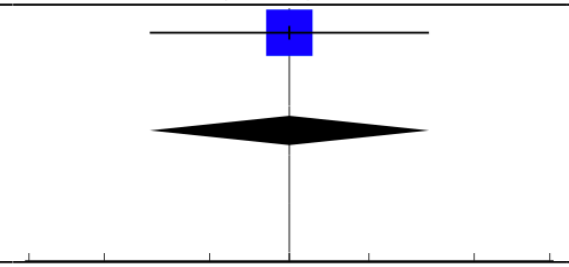
- Tocilizumab: Antagonist of IL-6
- Anakinra: Antagonist of IL-1
- Alemtuzumab: Anti CD-52

PLASMAPHERESIS AND LEUKOPHERESIS

- Conflicting results

Analysis 3.1. Comparison 3 Plasma exchange or leukapheresis versus placebo, Outcome 1 Number of patients who improved after treatment.

Study or subgroup	PE or leuka-pheresis n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Miller 1992	6/26	3/13		100%	1[0.3,3.37]
Total (95% CI)	**26**	**13**		**100%**	**1[0.3,3.37]**
Total events: 6 (PE or leukapheresis), 3 (Placebo)					
Heterogeneity: Not applicable					



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Conclusion

List of drugs currently used for idiopathic inflammatory myositis ad relative areas of effectiveness.

	Myositis	Interstitial lung disease	Arthritis	Cutaneous involvement
Glucocorticoids	●●●	●●●	●●●	●●●
High dose(s)*elim* Intravenous Immunoglobulins	●●●	●●	○	●●
Azathioprine	●●●	●●●	○	○
Methotrexate	●●●	!	●	●
Cyclosporine*	●●●	●●	●	○
Cyclophosphamide	●●●	●●●	○	●●
Mycophenolate	●●	●●●	○	●●
Hydroxychloroquine	!	○	●	●●●●
Rituximab	●●●	●●●	●	●●●

What is the best Tx plan?

1. High dose CS
2. Monthly IVIG
3. Triple therapy: High dose CS + IVIG + MTX
4. Cyclophosphamide

Take Home Massage:

Factors which are important for immunotherapy selection

- Clinical settings
- Histological findings
- Serologic status
- Co-morbidity
- Age
- Sex

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Thanks for your attention