別添１　多発（性）筋炎・皮膚筋炎治療ガイドライン（日本リウマチ学会承認版）

緒言

多発（性）筋炎（PM）および皮膚筋炎（DM）における治療ガイドラインに関しては、確立したものはない。治療ガイドラインは、治療に関する多くの論文を解析して、各論文にエビデンスレベルを付与し、科学的根拠に基づき治療に対する推奨を行い、確立した治療法をめざすものである。その根拠となる論文のレベル分類を表１に示す。PM/DM の治療に関しては、いまだに、ランダム化比較研究(RCT)がほとんど行われていない。つまり、エビデンスレベルが II 以上の論文から、推奨されるべき治療方法を導きだすことは不可能である。一方、論文の科学的根拠から、種々の治療法の推奨グレードがある（表２）。PM/DM の治療法の推奨は、参考となる論文のエビデンスレベルが低いことより、B あるいは C1 のグレードであり、治療法は多くの場合に治療医の専門分野、経験や知識に依存している。
そこで、本治療ガイドライン案では、神経内科、膠原病内科、皮膚科、各分野の専門家が合同で検討を重ね、広く受容される治療指針を作成することを目的とした。推奨する治療法は、日本の現状で行われていることを中心にしており、エビデンスレベルの低い治療方法も専門家の意見として取り入れた。この治療ガイドラインにより、どの分野においても共通の理解の上に治療が行われることが期待できる。なお、本ガイドラインは、個々の診療を妨げるものではなく、また、医療訴訟における根拠となるものでもない。

表１　エビデンスのレベル分類
I　　システマティック・レビューあるいはランダム化比較研究のメタアナリシス
II　　１つ以上のランダム化比較試験による
III　　非ランダム化比較試験による
IVa　　分析疫学的研究（コホート研究）
IVb　　分析疫学的研究（症例対照研究、横断研究）
V　　記述研究（症例報告やケース・シリーズ）
VI　　患者データに基づかない、専門委員会や専門家個人の意見

表２　ガイドラインにおける推奨グレード

A　　強い科学的根拠があり、行うよう強く勧められる
B　　科学的根拠があり、行うよう勧められる
C1　　科学的根拠がないが、行うよう勧められる
C2　　科学的根拠がなく、行わないよう勧められる
D　　無効性あるいは害を示す科学的根拠があり、行わないよう勧められる

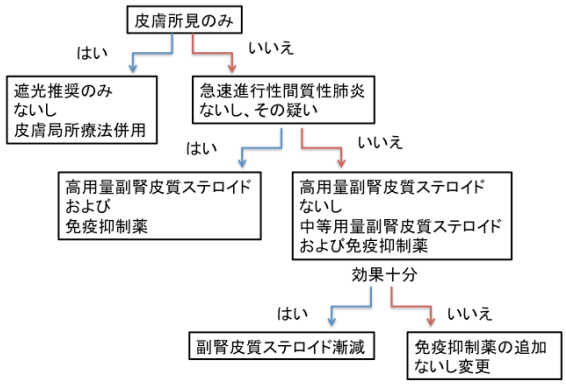

図　多発(性)筋炎・皮膚筋炎の初期治療
初期治療における原則的な治療方針の流れ図を示す。急速進行性間質性肺炎ないしその疑いのある場合には、高用量副腎皮質ステロイドと免疫抑制薬を同時に開始する。それ以外では、高用量副腎皮質ステロイドないし中等用量副腎皮質ステロイドと免疫抑制薬の併用を基本とする。効果が現れれば、副腎皮質ステロイドは漸減し、効果不十分例や副腎皮質ステロイド減量で再燃する例では、免疫抑制薬の追加や変更を行う。なお、皮膚所見のみの症例でも皮膚症状が著しい場合には全身療法を行う場合がある（CQ21 参照）。

CQ1. 機能予後や治療反応性を予測できる臨床症状や検査は何か

推奨文：臨床症状、検査所見により生命予後や治療反応性はある程度、推定できる。(推奨度 C1)

解説：臨床症状や一般検査で筋炎の予後や治療反応性を正確に予測することは困難であるが、経験的に治療反応性を規定する要因が知られている。
生命予後不良に関与する臨床背景・症状として、高齢(1, 2)、男性(3)、人種(非白人)(3, 4)、症状発現から治療までの期間(5, 6)、筋炎病型（癌関連筋炎、臨床的無筋症性皮膚筋炎）(5, 7)、皮膚潰瘍(7)、嚥下障害(4, 8)、呼吸障害（呼吸筋力低下・間質性肺炎）(8-10)、心病変(8)があげられる(エビデンスレベルⅢ-Ⅳ)。
高度の筋力低下を呈する場合、嚥下障害を伴う場合は一般に治療反応性は悪く、特に嚥下障害は生命予後を規定する要因の一つである(4, 8)。また、悪性腫瘍合併筋炎では治療反応性は悪いことが多いとさ

れている一方で、悪性腫瘍の摘出のみで筋炎が改善することも報告されているが、必ずしも当てはまらない場合もある。
血清 CK 値と治療反応性の関連については一定の見解はない。ただし、CK 値が異常高値を示す場合には正常化までに長期を要するために、反応性不良とされる可能性はある。
筋生検で筋壊死が強く炎症細胞浸潤が乏しい場合には治療反応性が悪いとされているが、これは抗 SRP 抗体陽性例である可能性がある(11,12)。

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CQ2. 自己抗体は有用な指標となるか

推奨文：筋炎特異（関連）自己抗体は筋炎の病型、病態、臨床経過、治療反応性と密接に関連しており、抗 Jo-1 抗体を含む抗アミノアシル tRNA 合成酵素抗体だけでなく、可能であれば種々の特異自己抗体の検索を行うべきである。(推奨度 A)

解説：筋炎に見出される筋炎特異抗体あるいは筋炎関連抗体の一部は筋炎および筋外合併症の治療反応性を予測できる可能性がある。

これらの自己抗体のうちで、抗 Mi-2 抗体、抗 U1RNP 抗体、抗 Ku 抗体陽性の症例は、比較的、副腎皮質ステロイド反応性が良好で生命予後も良いことが報告されている。ただし、後２者は筋炎オーバーラップ症候群でに認められる(1-7)（エビデンスレベルⅣ)。

抗 Jo-1 抗体およびその他の抗アミノアシル tRNA 合成酵素（ARS）抗体（抗 PL-7、PL-12、EJ、OJ、KS 抗体を含む）は筋炎とともに高頻度に間質性肺炎を合併する（抗 ARS 抗体症候群)。一般にこれらの抗 ARS 抗体陽性例の筋症状はステロイド抵抗性を示すことが報告されているが、一方で初期の治療には比較的良く反応するものの再燃率が高いとも報告されている。このことは間質性肺炎の治療反応性にも当てはまり、初期治療（副腎皮質ステロイド）反応性が期待できるが再燃率が高いため、呼吸機能の予後は必ずしも良好ではなく、再燃を防ぐために免疫抑制薬の併用が勧められる(8-10)(エビデンスレベルⅣ)。
抗 ARS 抗体の種類によっては臨床像・臨床経過・予

後に若干の差違が報告されている。抗 Jo-1 抗体とその他の抗体で比較されることが多く、抗 Jo-1 抗体陽性例では筋症状の頻度が多いのに対し、抗 PL-7、PL-12、KS 抗体陽性例では筋症状が比較的少ない。また間質性肺炎の頻度も抗 PL-7、PL-12、KS、EJ 抗体陽性例では抗 Jo-1 抗体陽性例よりも多い。予後も抗 PL-7/PL-12 抗体陽性例の方が抗 Jo-1 抗体陽性例よりも悪いとする報告がある(8, 11)(エビデンスレベルⅣ)。

抗 SRP 抗体は重症あるいは治療抵抗性、再発性筋炎のマーカーとして報告されている。同抗体陽性例は筋生検像で筋線維の壊死再生像が著明だが炎症細胞浸潤に乏しい壊死性筋症を示すことが報告されている。抗 SRP 抗体陽性筋炎は副腎皮質ステロイドに抵抗を示すことがあり、早期からの免疫抑制薬や免疫グロブリン大量静注療法を必要とする場合が多い(12, 13)(エビデンスレベルⅣ)。近年抗 SPR 抗体陽性の治療抵抗性例に対してリツキシマブの有効性が報告されている(14)(エビデンスレベルⅤ)。

抗 TIF-1γ/α (p155/140) 抗体は DM 全般に検出されるが、悪性腫瘍合併例では同抗体陽性率が高いことが報告されている。したがって同抗体陽性例には悪性腫瘍の徹底した検索と、慎重な経過観察を行うべきである(7)(エビデンスレベルⅣ)。

抗 MDA5 (CADM-140) 抗体は臨床的に筋症状がない皮膚筋炎 (臨床的無筋症性皮膚筋炎、CADM) に特異的な自己抗体であり、高率に急速に進行して死に至る予後の悪い間質性肺炎を合併することが多い(15, 16) (エビデンスレベルⅣ)。同抗体陽性 (あるいは陽性が疑われる) 例では早期から高用量副腎皮質ステロイドとともに免疫抑制療薬を同時に導入することが勧められる(17)(エビデンスレベルⅤ)。

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CQ3　血清 CK 値と筋力のどちらが筋炎の病勢を反映するか

推奨文：血清 creatine kinase (CK) 値と筋力はいずれも筋炎の病勢を評価する上で有用な指標である。(推奨度 B)

解説：Maillad ら(1)は活動期の小児皮膚筋炎 10 例と非活動期の 10 例について、大腿 MRI の T2 緩和時間のグレード、CMAS (childhood myositis assessment scale)、CHAQ (childhood health assessment questionnaire)、MMT、血清 CK 値、LDH 値を比較検討した。大腿 MRI の T2 緩和時間のグレードと MMT は相関するが、血清 CK 値、LDH 値は相関しないという結果が得られた(エビデンスレベルⅣb)。19 例の小児皮膚筋炎症例の大腿 MRI 所見と下肢近位筋 MMT、血清筋酵素 (CK、AST、aldolase [ALD]) の関係を検討した Hernandez らのケースシリーズ(2)では、T2 高信号比は MMT、血清筋酵素ともに有意な相関があるが MMT の相関がより強いと報告されている (エビデンスレベルⅤ)。
成人 102 例、小児 102 例の PM/DM 文献例をもとに、29 人の専門家によって定義された成人・小児 PM/DM の改善の指標として①physician's global activity、②patient's/parent's global activity、③筋力 (MMT で評価)、④physical function、⑤筋逸脱酵素 (CK, LDH, AST, ALT, アルドラーゼのうち最低２つ)、⑥extramuscular activity assessment、の 6 項目が示されている(3)。このうち 3 項目に 20%以上の改善がみられ、かつ 25%以上悪化した項目が２つを越えない場合を PM/DM の改善と判断する、としているが、6 項目の中で最も重視されているのは③筋力で、悪化項目に筋力が入った場合は改善とみなさない、と定義されている(エビデンスレベルⅥ)。筋炎の治療効果のモニター指標として MMT と CK の双方が重要である点に関しては専門家の意見はほぼ一致している。Engel and Hohlfeld(4)は、副腎皮質ステロイド薬治療に反応する場合は筋力より先に CK が低下し、悪化する場合は CK 上昇が筋力の増悪に先行すると記載し、CK 測定の有用性を述べている (エビデンスレベルⅥ)。一方、Dalakas(5)は炎症性筋疾患の治療のゴールは筋力と筋外症状 (嚥下障害、発熱、呼吸困難など) の改善であり、筋力改善があっても CK が相関しない場合、CK が低下しても筋力が改善しない場合があることを指摘している (エビデンスレベルⅥ)。PM/DM の免疫抑制療法・免疫調節療法に関する 2012 年のコクラン・レビュー(6)では、各治療法の有効性を評価する基準のうち primary outcome として採用されているのは①少なくとも 6 ヵ月後の機能または障害グレードの変化、②6 ヵ月後の 15%以上の筋力の改善の２つである (エビデンスレベルⅥ)。

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CQ4　PM/DM 治療の第一選択薬は何か

間質性肺炎を合併する場合→　CQ19
悪性腫瘍を合併する場合→　CQ25

推奨文：PM/DM 治療の第一選択薬は、副腎皮質ステロイドである。(推奨度 A)

解説：筋炎治療の第一選択薬としては、多くの専門家がプレドニゾロンを第一次治療薬として推奨しており、異論は少ない。臨床の場では、プレドニゾロンの使用が困難であるという状況を除いては、大部分の症例でプレドニゾロンが第一次選択薬として用いられている。 しかしながら、第一次選択薬としてのプレドニゾロン使用は経験に基づくものであり、有効性を前方視的なランダム化比較試験で示した報告はない(1-4) (エビデンスレベル VI)。
なお、本邦では副腎皮質ステロイドとして複数の経口薬と静注薬が使用可能であるが、その有効性に副腎皮質ステロイドの種類により差があるとする研究はない。ステロイドパルス療法にはメチルプレドニゾロンが用いられる。
なお、小児 DM では、副腎皮質ステロイドとメトトレキサートを初期治療から併用することで、副腎皮質ステロイドの早期漸減に有効であることが示されている(5) (6) (エビデンスレベル V)。
また、副腎皮質ステロイドにメチルプレドニゾロンパルス療法を併用した群で改善率が高く、CK の正常化までの期間が有意に短かったとする報告がある (7) (エビデンスレベル III)。
PM/DM には病態機序の異なるさまざまなグループが存在すると考えられ、副腎皮質ステロイドの有効性が乏しい状態として、高齢者、筋以外の臓器障害例（間質性肺炎、悪性腫瘍合併例）(1-4) (エビデンスレベル VI)、抗 SRP 抗体陽性例などが知られている (8, 9) (エビデンスレベル V)。 今後グループごと、患者ごとに第一選択薬を検討していく必要がある。

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CQ5　妥当な副腎皮質ステロイドの初期投与量はいくらか

推奨文：PM/DM の治療では、慣習的に体重 1kg 当たりプレドニゾロン換算 0.75～1mg で治療が始められている。(推奨度 C1)

解説：RCT は存在せず、専門家推奨に従って高用量副腎皮質ステロイドによる初期治療が行われるのが一般的である。しかし、免疫抑制薬の普及に伴い、より低用量での治療開始も選択肢となりつつある。実際に、プレドニゾロン初期投与量が 0.5 mg/体重 kg より多い（大部分が 1 mg/体重 kg）高用量群 15 人と、0.5 mg/体重 kg 以下の低用量群 10 人（ほぼ全例で免疫抑制薬併用）の 2 群について CK や筋力などを比較した症例対照研究(1)がある。両群とも治療前の CK は同レベルであり、主治医判断で行った治療後の CK や筋力などの筋機能も両群に有意差を認めなかった。プレドニゾロンによる副作用は、低用量群がより少ない傾向にあり、椎体圧迫骨折患者数で有意差が認められた。この研究では、両群の治療前の筋力低下の程度が不明で、ステロイド筋症の関与も不明である。しかし、少なくとも免疫抑制薬併用下では、プレドニゾロン初期投与量が 0.5mg/体重 kg 以下でもよいことを示唆している。
　副腎皮質ステロイド減量の時期に関する RCT は無いが、副腎皮質ステロイドにより筋症が生じる可能

性があるため、2週間から4週間の初期投与量での治療後は、筋炎に対する治療効果により、週に5-10mgの減量を行っていく。なお、副腎皮質ホルモン単独療法よりも免疫抑制療薬併用療法の方が、副腎皮質ステロイド減量が容易である場合が多い(2)。
投与方法は、1日3分割の連日投与が一般的である。副腎抑制を懸念し、隔日投与もしくは朝1回の投与が行われることもある。しかし、このような投与方法でも中等量以上の副腎皮質ステロイドを使用すれば、副腎抑制を免れることは難しく、また3分割の連日投与に比べ治療効果が劣る。低用量まで減量した場合には、朝1回投与や隔日投与とすることを考慮する。

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CQ6　副腎皮質ステロイドによる治療によって、治療前に比べて、いったん萎縮した筋が回復することはあるか

回答：いったん萎縮した筋量が回復することは期待できる。

解説：骨格筋量は骨格筋線維の蛋白質の合成（同化）プロセスと分解（異化）プロセスのバランスにより決定され、バランス調整には、ホルモン、栄養物質、サイトカイン、物理的張力などの様々なシグナルが関与する(1)（エビデンスレベルⅥ)。
副腎皮質ステロイド投与で筋炎の筋力が回復する機序としては、副腎皮質ステロイドにより炎症に伴う筋線維破壊が抑制され筋再生が優位になるためと考えられるが(2)(3)（エビデンスレベルⅥ）、一方で副腎皮質ステロイドでは骨格筋の異化が生じることが知られている(4)（エビデンスレベルⅣ)。　過去に筋炎において副腎皮質ステロイド治療による筋量の変化を検討した報告はなく、いったん萎縮した筋量が回復することは期待されるがエビデンスレベルの高い報告は存在しない。

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CQ7. 寛解後に副腎皮質ステロイドを中止することが可能か

回答：副腎皮質ステロイド中止が維持療法持続に比べて再燃率が高いか否かを示すデータはないが、一部の症例では副腎皮質ステロイド中止が可能である。

解説： PM/DMにおいて薬剤を中止した完全寛解に至る率は、25%-87%と報告により様々である1, 2。これには病型や初期治療をはじめとする多様な因子が関係していると考えられるが、多くの研究ににおいて40-60%の寛解率が報告されていることは、症例によっては副腎皮質ステロイドの中止が可能であることを示す。
Phillipsらの報告(エビデンスレベルIVb)では、DM23例、PM9例、オーバーラップ18例の経過についての後ろ向きの検討で、再燃はPM67%、DM65%、オーバーラップ50%にみられ、複数回の再燃はDM60%、オーバーラップ67%、PM33%であった3。各疾患群で再燃がもっとも多かったのは低用量の維持療法の時期であったが（PM 46%, DM 38%, オーバーラップ77%)、治療終了後に起きた例も多かった（PM 23%, DM 18%, オーバーラップ5%)。
Marieらは、77例のPM/DMの経過を18ヵ月以上(死亡例を除く)、後ろ向きに検討し、40%が寛解に至ったと報告している。また、18%が一峰性の経過をとり、64%が慢性持続性の経過を示した。58%に再燃がみられ、高用量副腎皮質ステロイドの減量中または維持療法中が27%、低用量（20mg/日）の副腎皮質ステロイドの減量中が19%、治療終了後が12%であった（エビデンスレベルIVb)。
これらの報告から低用量が投与されていても再燃

する症例が存在することは明らかであるが、PM/DM において維持量の副腎皮質ステロイド内服継続した群と中止した群の再燃率を直接比較することは不可能である。

副腎皮質ステロイドの維持療法が必要となるような慢性の経過をとる群のリスク因子として、Bronner らによる PM/DM の長期予後調査では、110 例において中央値 5 年の追跡を行い、41%が 10mg/日以上のプレドニゾンまたは免疫抑制薬の治療中であり、抗 Jo-1 抗体陽性は治療継続のオッズ比が有意に高かったと報告している 4（エビデンスレベル IVb)。したがって、抗 Jo-1 抗体を含む抗アミノアシル tRNA 合成酵素抗体症候群では、治療継続の必要性がある症例の比率が高い可能性がある。Marie らは、抗 Jo-1 抗体陽性群と抗 PL-7/PL-12 抗体陽性群とで比較を行い、筋炎の寛解率は抗 Jo-1 抗体陽性群で 21.3%、抗 PL-7/PL-12 抗体陽性群で 46.2%であったが、間質性肺病変の寛解率は抗 Jo-1 抗体陽性群で 29.4%、抗 PL-7/PL-12 抗体陽性群で 5.6%であったと報告している 5（エビデンスレベル IVb)。したがって、自己抗体の違いによって、治療継続の対象となる病態が異なる可能性がある。

以上より、現時点では、どのような症例で副腎皮質ステロイド維持療法が必要か、あるいは副腎皮質ステロイドの中止が可能かを一般的に分類することは困難であり、治療継続の是非は個々の症例の経過をもとに判断すべきである。

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CQ8　PM/DM による筋力低下とステロイド筋症による筋力低下はどのように鑑別するか

回答：PM／DM による筋力低下とステロイド筋症による筋力低下を鑑別は、臨床像と検査所見を参考にして総合的に判断する。

解説：筋炎治療のために長期間の副腎皮質ステロイド投与中に CK が正常またはそれ迄と同じ程度の値をとりながら筋力低下が進行する場合にステロイド筋症を疑う(1, 2)(エビデンスレベル V)(エビデンスレベル VI)。 しかしながら、ステロイド筋症はしばしば筋炎の再燃と共存し、廃用性筋萎縮、栄養状態悪化、感染などの全身状態悪化も加わると判断が難しくなる場合も多い。
ステロイド筋症を発症する副腎皮質ステロイド投与量や副腎皮質ステロイド投与から発症までの期間には個人差がある。一般にプレドニゾロン相当で 10mg/日の投与量で生じることは少ないとされ、40～60ｍｇ/日の投与により 2 週間で生じ、1 ヶ月の投与で一定の程度の筋力低下を認めるとの報告がある(3)(エビデンスレベル III)。また、悪性腫瘍合併患者や高齢者にてリスクが高い(4)（エビデンスレベル VI)。患者は、しばしば、副腎皮質ステロイドによる他の副作用である満月様顔貌、糖尿病、中心性肥満、精神症状、皮膚変化、骨粗鬆症を伴うことが多い(3)(エビデンスレベル III)。
筋力低下は、近位筋優位で遠位に生じることは稀で、上肢よりも腰帯筋にめだつ傾向がある(3, 5)（エビデンスレベル III)(エビデンスレベル VI)。
針筋電図では筋原性変化を認め安静時放電は認めないため筋炎の再燃との鑑別に有用である(1, 4, 6)(エビデンスレベル V)（エビデンスレベル VI)（エビデンスレベル VI）。
ステロイド筋症では 24 時間尿中の creatine 排泄が増加しており判断の上で参考になるという報告もあるが(1)（エビデンスレベル V)、必ずしも役立たないとの報告もある。(3)（エビデンスレベル III)。
筋病理では選択的な Type2 線維の萎縮を認める(4, 7, 8)（エビデンスレベル VI)（エビデンスレベル IV)(エビデンスレベル IV)。骨格筋 MRI の脂肪抑制 T2 強調画像で高信号への変化を認める場合には再燃を疑うが(9)（10)（エビデンスレベル VI)(エビデンスレベル VI)、過度の運動負荷が加わった筋でも同所見を認めることがあるため充分に安静にした上での評価が必要である。
ステロイド筋症の診断に際しては、先行する 2 ヶ月前までの、筋力の経過、CK 値の変化、検査所見、治療内容を総合的に考え判断する必要がある(2)（エ

ビデンスレベル VI)。副腎皮質ステロイドの投与量を減量して 2〜8 週間、その後の筋力の経過を追うことにより判断することが必要になる場合もある(2)(エビデンスレベル VI)。ステロイド筋症は適切な量のステロイドの減量により 3〜4 週後に改善する(3)(エビデンスレベル III)。

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CQ9　免疫抑制薬の併用は、どのような症例で検討すべきか

推奨文：第一選択治療薬である副腎皮質ステロイドに治療抵抗性の筋炎に対して免疫抑制薬を併用するべきである（推奨度 B）

PM/DM の治療には、副腎皮質ステロイド薬単独ではなく、早期からメトトレキサート、アザチオプリン、タクロリムス、シクロスポリン A のどれかの免疫抑制薬を併用して治療を考慮して良い（推奨度 C1）

解説：1950 年代から筋炎の標準的な治療は、副腎皮質ステロイドの高用量投与である。副腎皮質ステロイドの単独での治療では、有効でない症例や有効性が認められた症例でも副腎皮質ステロイドの減量に伴い再燃が認められることがある。2010 年の van de Vlekkert らの論文では、副腎皮質ステロイドの単独治療で、45%程度の症例で再発が認められた（エビデンスレベル II)。

初期治療としての高用量副腎皮質ステロイド投与には多くの症例が反応するが、その減量に伴い再燃が認められる症例が少なくない。これらの症例では、免疫抑制薬の併用が行われる。

一方、副腎皮質ステロイドでの治療が長期におよぶとステロイド筋症を引き起こされ、筋力の回復が困難となる。そのため、大量の副腎皮質ステロイドの使用は、できるだけ短期にすることが必要である。再発例では、副腎皮質ステロイドの増量を考慮する必要が生じる。

これらのことを考えると、副腎皮質ステロイドの初期投与量の時期から、有効性が認められているメトトレキサート（保険適応外)、アザチオプリン、タクロリムス、シクロスポリン A（保険適応外）のどれかの併用は、治療効果があり、さらに、副腎皮質ステロイドの減量に伴う再燃の率を低下させると考える（エビデンスレベル VI)。

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CQ10 免疫抑制薬の併用は副腎皮質ステロイドの早期減量を可能にするか

回答：免疫抑制薬の併用は副腎皮質ステロイドの早期減量に有用である

解説：多施設 RCT などは存在しないものの、副腎皮質ステロイドの使用量に言及している比較的エビデンスの高い研究として、Bunch らが筋症状に対してプレドニゾン投与中の PM16 症例に無作為にアザチオプリンを併用した結果、3 年後に併用群でプレドニゾンの投与量が有意に減少した(1.6 mg/day vs 8.7 mg/day)というものがある(1) （エビデンスレベル II)。その他、様々な症例報告が免疫抑制薬の併用による副腎皮質ステロイド早期減量効果を示唆しているが多数例の解析として、Qushmaq らが治療抵抗性の筋症状を有する PM/DM6 例に対して平均 3.5mg/体重 kg/day のシクロスポリン A(保険適応外)を平均 6 ヶ月間投与し,副腎皮質ステロイド量を 75%程度減量している(2) （エビデンスレベル V)。加えて 14 例の治療抵抗性の小児 DM の検討では平均 3 年のシクロスポリン A 併用で筋症状などの改善とともに副腎皮質ステロイドの減量が可能になっている(3) （エビデンスレベル V)。
また、Wilkes らは 13 例の間質性肺炎を伴う抗 ARS 抗体症候群に対してタクロリムス（PM/DM に伴う間質性肺炎治療に保険適応）を約 51 ヶ月投与し、筋症状や肺症状の改善とともに平均 67%の副腎皮質ステロイド減量を可能にしている(4) （エビデンスレベル V)。
ミコフェノール酸モフェチル（保険適応外）についても、50 例の小児 DM で筋症状や皮膚症状の改善とともに副腎皮質ステロイドの投与量を有意に減量させている(5) （エビデンスレベル V)。さらには 12 例の DM の皮膚症状に対する副腎皮質ステロイドの投与量を 93%と大幅に減量したり(6) （エビデンスレベル V)、DM 10 例中 6 例で副腎皮質ステロイド減量効果を認めたという報告がある(7) （エビデンスレベル V)。
メトトレキサート（保険適応外）に関しては、31 例の小児 DM の筋症状に対して併用した場合に併用しなかった 22 例と比べて副腎皮質ステロイドの投与期間・量を有意に減少させている(8) （エビデンスレベル V)。あるいは 13 例の DM の皮膚症状に対しての副腎皮質ステロイドの量を減少させたことが報告されており(9) （エビデンスレベル V)、さらに無筋症性 DM(ADM)においても 2 例でメトトレキサートの併用により平均 13 週後に副腎皮質ステロイド投与量が約半分になったという報告もある(10) （エビデンスレベル V)。
以上のように，各報告のエビデンスレベルは高くないものの、様々な免疫抑制薬が steroid-sparing agent として副腎皮質ステロイドの早期減量を可能にしていると考えられる。

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CQ11 副腎皮質ステロイド以外に用いる免疫抑制薬は何か

推奨文：検討が行われている薬剤は、アザチオプリン、メトトレキサート、タクロリムス、シクロスポリンA、ミコフェノール酸モフェチル、シクロホスファミドである。本邦で、良く使用されるのは、アザチオプリン、メトトレキサート（保険適応外）、タクロリムス、シクロスポリンA（保険適応外）、である。（推奨度B）

解説：
アザチオプリン（AZA）
推奨度：B
解説： 1980年ごろに、副腎皮質ステロイド薬との併用療法での有効性が報告された(1, 2)。小児皮膚筋炎に対して、MTXまたはAZAを初期治療として用いることで、生存率の改善がみられている。AZAは筋炎再燃時に選択される薬剤の1つと考えられる。（保険適用）
投与量　50-100mg/日　分1- 2投与

メトトレキサート(MTX)
推奨度：B
解説：筋炎再燃に対してMTXの有用性が報告されている(3, 4)。小児皮膚筋炎では、1つのランダム化比較試験を含む臨床試験から、副腎皮質ステロイドとMTXを初期治療から使用することで、副腎皮質ステロイドの早期漸減に有効であることが示された。MTXは筋炎再燃時に選択される薬剤の1つと考えられる。本邦では保険適応ではないが、MTXの有用性はよく経験されることである。
投与量　7.5-15 mg／週に一日投与

タクロリムス(Tac)
推奨度：B
筋炎再燃に対するTacの有効性が報告されている(8-10)。副腎皮質ステロイドとTac併用群は副腎皮質ステロイド単独療法群に比べCK、ALDおよびMMTを有意に改善させ、Tacは筋炎再燃時に有効な薬剤と考えられる。なお、筋炎に合併した間質性肺炎についても有効性が報告されており、CsA無効例にもTacが有効であることが示されている。(PM/DMに伴う間質性肺炎治療に保険適用)
投与量　至適トラフ濃度 5-10 ng/mlに達するように分2投与

シクロスポリンA（CsA）
推奨度：B
1つのランダム化比較試験があり、CsAは副腎皮質ステロイドの早期漸減に有効であることが示されており（5)、筋炎再燃時の治療の選択肢となりえる。なお、間質性肺炎合併例についても、CsAと副腎皮質ステロイドの併用は副腎皮質ステロイド単独治療に比べ、筋炎に合併した間質性肺炎の予後を改善させることが知られている(6, 7)。
投与量　至適トラフ濃度 100-150 ng/mlに達するように分2投与
（投与2時間値 1,000 ng/mlを目標として分1投与する方法も用いられる）

ミコフェノール酸モフェチル（MMF）
推奨度：B
筋炎再燃に対するMMFの有効性が報告されている(11-13)。また小児皮膚筋炎50症例の検討では皮膚炎および筋炎の活動性指標、筋炎の活動性を有意に低下させた(13)。したがって、MMFは筋炎再燃時の有効な薬剤の1つと考えられる。本邦では保険適応ではないが、MTXの有用性はよく経験されることである。
投与量　1-3 g／日、分2投与

シクロホスファミド（CPA）
推奨度：C1
他の膠原病・リウマチ性疾患に比してCPAが使用されることは希である。しかし、再発性筋炎の治療にCsAの代用薬として有効と報告され、合併する間質性肺炎にも用いられる(14)。従って、難治性筋炎や筋炎再燃の治療に使用できると考えられる。(保険適用)
投与量　50-100mg/日　分1- 2投与
ないし　体表面積m2当たり500mg程度/回を4週毎に点滴静注

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CQ12 副腎皮質ステロイド抵抗例では IVIg による治療を考慮すべきか

推奨文：副腎皮質ステロイドが十分に奏効しない DM 症例（グレード B)、PM 症例（グレード C1）では IVIg による治療を考慮してよい。

解説:PM/DM を対象とした 2 つの RCT がある。Dalakas ら(1)は筋生検で確定診断(2)したステロイド抵抗性の DM 患者 15 例を、プレドニゾン＋プラセボ群（7 例)、プレドニゾン＋IVIg 群（8 例、1g/kg/日 2 日間投与、月 1 回で 3 ヶ月間）の 2 群に無作為に割り付けた二重盲検比較試験を行い、一部の患者はクロスオーバー試験に移行した。プレドニゾン＋IVIg 群で投与 3 ヵ月後の筋力(MRC スコア)、皮疹、血清 CK 値、筋生検所見で有意な改善が得られた（エビデンスレベルⅡ)。
Miyasaka ら(3)は Bohan and Peter の診断基準(4) (5)を満たすステロイド抵抗性 PM/DM26 例を IVIg 群(12 例、0.4g/kg/日 5 日間投与）とプラセボ群（14 例）の 2 群に無作為に割り付けた二重盲検クロスオーバー試験を行った。IVIg 群で徒手筋力テスト、血清 CK 値、日常生活スコアで有意な改善が得られたが、プラセボ群でも有意な改善があり、2 群間の有意差は見いだせなかった（エビデンスレベルⅡ)。
Danieli らによる症例対照研究では、プレドニゾンとシクロスポリン A で加療されている PM8 例、DM12 例を対象とし、併用治療無し 7 例、IVIg (1g/kg/日 2 日間投与, 12 ヵ月継続）併用（7 例)、IVIg（1g/kg/日 2 日間投与, 12 ヵ月継続）プラス血漿交換療法を併用(6 例)、の 3 群に分けた比較検討が施行された。4 年間の経過観察で IVIg 併用群は非併用群と比較して高い寛解率が得られた。血漿交換療法の上乗せ効果はなかった（エビデンスレベルⅣb)。
IVIg 療法の効果を検討したケースシリーズ、1 例報告は多数あり、多くの報告で筋力スコア、血清 CK、ADL スコアの改善をみている。いくつかのケースシリーズは嚥下障害の改善に言及しており(6) (7)（エビデンスレベルⅤ)、IVIg 療法が行われた患者の完全寛解率は 34.3% (8)（エビデンスレベルⅤ）から 100%(ミコフェノール酸モフェチルを併用）(9)（エビデンスレベルⅤ）である。
アメリカ神経学会が 2012 年に出版した神経筋疾患の IVIg 療法に関する治療ガイドライン(10)では、治療無反応性 DM はレベル C (IVIg 治療を考慮する可能性がある)、PM はレベル U（エビデンスが不十分）と記載されている（エビデンスレベルⅥ)。

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CQ13　治療強化の検討を要する筋炎再燃の指標は何か

推奨文：筋原性酵素 CK, ALD の上昇、および筋力評価が一般的に用いられる。その他にも画像所見や Visual analog scale、針筋電図所見なども指標となる。しかし、様々な指標を総合的に考慮する必要があり、これらを総合した疾患活動性指標も提唱されている（推奨度 B)。

解説：
筋原性酵素
推奨度：B
解説：筋炎再燃の定義はなく明確なエビデンスはないものの CK、ALD が筋炎再燃の基準のひとつとして用いられている。多くの疫学研究では CK、ALD を含め医師が総合的に筋炎再燃と診断した症例もしくは副腎皮質ステロイド薬に治療抵抗性の筋炎症例を対象に、免疫抑制薬などの効果を CK、ALD を用い疾患活動性を観察している。1993 年から 2012 年までの間に主要な雑誌に 26 の疫学研究が掲載され、全研究で CK、ALD が用いられており(1-26)、CK、ALD は筋炎再燃時の指標と考えられる。

Manual Muscle Testing (MMT)
推奨度：B
筋炎再燃の定義はなく明確なエビデンスはないものの MMT が筋炎再燃の基準のひとつとして用いられている。多くの疫学研究では MMT を含め医師が総合的に筋炎再燃と診断した症例もしくは副腎皮質ステロイド薬に治療抵抗性の筋炎症例を対象に、免疫抑制薬などの効果について MMT を用いた疾患活動性で観察している。1993 年から 2012 年までの間に主要な雑誌に掲載された 26 の疫学研究のうち 23 で MMT が用いられている(4-7, 9-26)。MMT は CK、ALD に次いで筋炎再燃時の指標として使用されており、治療強化を要する際の指標の 1 つと考えられる。ただし、副腎皮質ステロイド薬投与下では、ステロイド筋症による筋力低下を考慮する必要がある。

核磁気共鳴画像 (MRI)
推奨度：C1
解説：1991 年に STIR 画像が筋炎の活動性の指標になると報告され(27)、近年では筋炎再燃時の指標の 1 つとして使用されている(28)。T2 強調脂肪抑制 MRI 画像も筋炎の活動性の指標になると報告がある(28)。

Visual analog scale (VAS)
推奨度：C1
解説：近年では小児皮膚筋炎の皮膚病変と 10 cm

visual analog scale (VAS)が強く相関することが報告された(29)。またVASは国際的な筋炎の臨床研究グループであるinternational myositis assessment & clinical studies group (IMACS)でも使用されている。

針筋電図
推奨度：C1
解説：針筋電図は筋炎の診断に有用な検査方法であるが(30)、筋炎再燃時の指標としても有用であると1つの症例報告で記載されている(31)。

IMACSコアセット
推奨度：C1
解説：筋炎悪化の定義について、IMACSでは以下の6つの指標のうち3項目が30%以上低下した場合としている(32)。1. physician global disease activity, 2. parent/patient global disease activity, 3. manual muscle strength testing (MMT), 4. physical function, 5. laboratory measurements and 6. extramuscular disease complications (http://www.niehs.nih.gov/research/resources/collab/imacs/index.cfm)
現在迄に本指標を用いた臨床研究は少ないが (33, 34)、総合指標として今後は普及する可能性がある。

Functional index
推奨度：C1
解説：Functional index (FI) は、指定された動作を一定の回数、一定の速さで反復することで筋の持久力を測定する検査方法であり1996年にJosefsonら(35)が炎症性筋疾患における筋力評価システムとして報告した。さらに今日では、簡略化したFunctional index 2 (FI-2)も用いられており、PM/DM症例において身体機能の改善と相関することが示されている(36)。これを再燃の指標として用いた報告はないものの、既にいくつかの臨床研究において検査の一部が評価項目として用いられている。

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CQ14 筋炎再燃の場合に選択される治療方法は何か

推奨文：筋炎再燃時には副腎皮質ステロイドを増量（0.5-1.0 mg/体重 kg)、または、免疫抑制薬、大量免疫グロブリン静注療法、生物学的製剤（トシリズマブ、アバタセプト、リツキシマブ、TNF 阻害薬)、血漿交換の追加または併用が行われている。

解説：
副腎皮質ステロイドの増量
推奨度：B
解説：筋炎再燃時には副腎皮質ステロイドの増量（0.5-1.0 mg/体重 kg)、免疫抑制薬の追加ないし変更がなされる(1-3)。しかし、増量すべき副腎皮質ステロイドの量についてのエビデンスはなく、副作用などで副腎皮質ステロイドの十分な増量が困難な場合は、積極的に免疫抑制薬を併用することが望ましい。

免疫抑制薬
詳細は、CQ11 を参照

大量免疫グロブリン静注療法（IVIg)
推奨度：B
筋炎再燃もしくは重症筋炎に対して IVIg の有効性は多数報告されている(5-6)。筋炎再燃に対する IVIg 治療は再燃率を有意に低下させ、長期予後の改善に繋がることが示されている(4-6)。また間質性肺炎合併筋炎や嚥下障害を呈する筋炎についても、IVIg の有効性が報告されている(7, 8)。持続的効果を得るには反復投与が必要ながら、筋炎再燃時に選択うる薬剤の 1 つと考えられる。(保険適用)

トシリズマブ
推奨度：C1
近年、2 症例の多発性筋炎患者にトシリズマブが有効であったことが報告され、トシリズマブが筋炎再燃時の治療に有効であることが示唆された(9)。筋炎の病因における IL-6 の役割は明らかではないが、IL-6 は疾患活動性のマーカーとしても有効であることが報告されている(10)。

アバタセプト
推奨度：C1
筋炎再燃、難治例に対して 2 つの症例報告で有効性が報告されている(11, 12)。今後の症例の蓄積が必要である。

リツキシマブ
推奨度：グレードなし
いくつかの uncontrolled trial や記述研究で有効性が報告されている(13-17)。しかし、近年行われた 200 例の PM/DM を対象にリツキシマブの有効性を検討したランダム化比較試験(18)では投与群とプラセボ群の 2 群間に有意差が認められず、筋炎再燃に対する本薬の有効性が証明されなかった。

TNF 阻害薬
推奨度：C2
抗 TNF✔抗体を用いた uncontrolled trial では 8 例中 6 例の筋炎再燃に対して抗 TNF✔抗体治療の有効性が認められた(19)。しかし、その後のいくつかの臨床試験で筋炎再燃に対する抗 TNF✔抗体治療の有効性は否定され(20, 21)、さらに抗 TNF✔抗体治療後に筋炎が発症した症例も報告されており(22,23)、治療薬としての妥当性は未確定である。

血漿交換
推奨度：C2
筋炎再燃に対して症例報告での有用性が報告されているが(24)、ランダム化試験の結果、筋炎再燃に対して有効性は認められなかった(25)。

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CQ15 間質性肺炎に副腎皮質ステロイドや免疫抑制薬で治療する場合に日和見感染症対策は必要か

推奨文：間質性肺炎に副腎皮質ステロイド大量療法や免疫抑制薬を投与する際、ニューモシスチス肺炎などの日和見感染症への対策が必要である。(推奨度 A)

解説：フランスの PM/DM を対象とした 156 例、279 例において日和見感染症を発症した症例は、それぞれ 18 例(11.5%)(1)、33 例(11.8%)(2)であった（エビデンスレベル IV)。原因菌は真菌類が最多で、中でも Candida albicans、Pneumocystis jiroveci が多かった。前者の研究では日和見感染症発症者の末梢血リンパ球数、血清総タンパク濃度は非発症者に比べて有意に低かった。また、発症した 18 例中 2 例は副腎皮質ステロイドも免疫抑制剤も非使用例であったが、他は副腎皮質ステロイドが様々な用量で投与されており､7 例は免疫抑制剤が併用されていた。プレドニゾロン 40mg/日以上投与された 75 例の SLE および PM/DM 患者を集計した成績では、7 例(9.3%)にニューモシスチス肺炎が併発し、全例が間質性肺炎の合併例であった(3)（エビデンスレベル IV)。ST 合剤の予防投与がなされていた症例では、ニューモシスチス肺炎の発症は無かった(4)(エビデンスレベル IV)。
2011 年の American Thoracic Society の勧告では、免疫抑制治療を行う患者において、プレドニゾロン 20mg/日を超える用量を一ヶ月以上使用する場合、特に免疫抑制剤を併用する場合は、ST 合剤の 1 日 1 錠連日ないし 2 錠を週 3 日投与することが推奨されており(5)、間質性肺炎治療に際しては、ニューモシスチス肺炎予防を目的として上記投与が推奨される（エビデンスレベル VI)。
肺結核の予防に関しては、HIV 感染患者に準じた予防的措置を講じる。陳旧性肺結核病巣のある患者には、イソニアジドなどの予防投与を行う(6)（エビデンスレベル VI)。

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CQ16 治療早期からのリハビリテーションは有効か

推奨文：治療開始早期からのリハビリテーション開始は筋力回復に有効である報告があり、有害であるとする報告はないため施行しても良いが、最終的な機能予後の改善効果については明らかではない。また、リハビリテーションの際の最適な負荷の程度も明らかではない。(推奨度 C1)

解説：PM/DM の治療開始早期にリハビリテーションを併用した際の効果や有害事象について検証した RCT や大規模な研究はなく、いくつかの小さなケースシリーズの報告がある程度である。Alexanderson ら(1)は 11 例の発症後間もない PM/DM 患者に対し 12 週間の resistive training を課したところ、CK の上昇などを伴わず ADL や機能の回復が見られたと報告している（エビデンスレベル V)。
また、Escalante ら(2)は 5 例の PM/DM 患者を対象として 4 例は resistive、nonresistive の両エクササイズを、1 例は resistive のみのエクササイズを施行した。MMT や ADL スコア、下肢の peak isometric torque などを評価した結果によると、前者のうち 3 例が両エクササイズでの効果を認め、残り 1 例は無効であった。resistive のみのエクササイズを行った 1 例も筋力の改善を認めた。また、これら何れの

エクササイズの際にもCKの有意な上昇は認めなかった。(エビデンスレベルV)
以上のような結果はあるが、いずれの報告も対照群を置いた研究ではなく、リハビリテーション施行の有無による機能予後の変化については明らかではないが、リハビリテーションが有害であるとする研究結果はない。
また、負荷の程度により機能予後が変化するかどうかについても検討した研究はなく、適切な負荷の程度についても明らかではない。

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CQ17 慢性期の筋炎患者の筋力低下はリハビリテーションで回復するか

推奨文：慢性期のリハビリテーションは炎症の悪化を伴わず筋力回復に有効である可能性があり、行うことが勧められる（推奨度B)

解説：PM/DMの慢性期にリハビリテーションを行った際の効果、有害事象などについては小規模なRCTがいくつか行われている。Wiesingerら(1)は14例のPM/DM患者に対して自転車漕ぎや踏み台昇降の運動負荷を6週間にわたって施行し、運動負荷を施行しない対照群と比べてADLスコアや下肢の筋力、筋のピーク酸素消費量が有意に増加することを示した。この際にCKの上昇や炎症の悪化は見られなかった。また、彼らは期間を６ヶ月間に延長したRCT(2)も実行しており、こちらでも有害事象を生じることなく筋力やADLスコアの向上が示されている。
また、RCTではないがAlexandersonら(3, 4)は慢性期のPM/DM患者群に対し運動負荷を施行し、筋力やADLスコアの向上が見られた際に生検筋を用いて炎症所見の悪化が見られなかったことや筋MRI所見の悪化が見られなかったことを報告している。

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CQ18 嚥下障害を伴う場合の治療法は何か

推奨文：副腎皮質ステロイド薬抵抗性の嚥下障害に対しIVIg療法は試みられてよい治療法である。(推奨度Ｃ１)

解説：PM/DMの嚥下障害の治療に関するRCTや比較対照試験はなく、ケースシリーズないし症例報告での記載がほとんどである。比較的大規模な2つのケースシリーズが報告されている。Marieら(1)（エビデンスレベルⅤ）はステロイド抵抗性の嚥下障害をきたし、IVIg治療がなされたPM/DM73例（PM39例、DM34例、Bohan and Peter基準(2, 3)で診断）を後方視的に解析した。1g/kg/日ｘ2日間のIVIgを1クールとして毎月施行（平均治療期間は7ヵ月)、全例に嚥下リハビリテーションが併用された。27例が2クール終了後5-15日以内に、33例が5-15日以内に経口摂取可能となった。4例は治療に反応したが軽度の嚥下困難が間歇的に出現、1例は輪状咽頭筋切断術を要した。8例はIVIgに反応せず、誤嚥性肺炎（6例）と癌（2例）で死亡した。
Ohら(4)（エビデンスレベルⅤ）は嚥下障害をきたしたMayo Clinicの筋炎患者62人(1997-2001年、IBM26例、DM18例、PM9例、overlap syndrome9例、PM/DMはDalakas基準(5)で診断)を後方視的に解析した。IBM20例、DM17例、PMとoverlap syndrome全例でステロイド、アザチオプリン、メトトレキサートなどの免疫抑制療法が施行されており、IVIgはIBM1例、DM4例、PM2例、overlap syndrome1例に施行された。IBMでは輪状咽頭筋切断術などの外科的治療介入が施行された例が多かったが嚥下障害が寛解した例はなく、DM6例、PM1例、overlap syndrome4

例で嚥下障害は寛解した。
Palace ら(6)は 3 年間にわたって嚥下困難のみが症状で、プレドニゾロン 40mg の内服が有効であった 69 歳 PM 女性例を報告している（エビデンスレベルⅤ）。
小規模なケースシリーズ、症例報告レベルでは、IVIg(7-9)（エビデンスレベルⅤ）、シクロスポリン(10)（エビデンスレベルⅤ）、シクロホスファミド＋メトトレキサート(11)（エビデンスレベルⅤ）、輪状咽頭筋切断術(12, 13)（エビデンスレベルⅤ）、内視鏡下バルーン拡張術(14)（エビデンスレベルⅤ）などの有効性が報告されている。

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CQ19 間質性肺炎が合併する場合の治療法は何か

推奨文：副腎皮質ステロイド大量療法（プレドニゾロン 1mg/体重 kg）を基本とし、CADM に伴う間質性肺炎（IP）のような難治性 IP ないし、それが予想される場合には、初期から免疫抑制薬を併用する。（推奨度 B）

解説：PM/DM の約半数に IP を合併する(1)。治療方針を決める際に筋炎自身の治療だけでなく IP の治療を考えなくてはならない場合も多く、いずれの病態の治療を優先するか、あるいは重点を置くべきかを検討する必要がある。通常は両者を同時に治療の対象とする場合が多い。しかし、IP の予後と治療反応性は筋炎の病型、画像所見（HRCT)、病理組織所見および自己抗体の種類によって異なるので、可能な限りこれらの情報を収集すべきである(1-6)(エビデンスレベル IV)（推奨度 B)。一般に DM に合併する IP は PM に合併する IP よりも予後が悪い(7-9)(エビデンスレベル IV)。

PM/DM に合併する IP にはステロイド大量療法（プレドニゾロン 1mg/体重 kg/day)が有効な場合が多く、まず PM/DM の治療と同様にステロイド単独療法の反応性を確認する(1)（エビデンスレベル IV-V)。しかし、難治性あるいは再燃を繰り返す IP も少なくない

ため、免疫抑制薬を併用すべき症例は多い。特にCADMに合併する急速進行性IPは治療抵抗性で死亡率が高いため、当初からステロイド大量療法とともに強力な免疫抑制療法の導入が勧められる(1)(エビデンスレベル IV-V)。経過や予後予測のマーカーとしてはPaO2/FiO2比やA-aDO2の値(5, 10, 11)、KL-6やSP-Dの推移(12)、抗MDA5抗体の存在やその抗体価の推移(11-15)、フェリチン値やその推移(11)などが有用である（エビデンスレベルIV-V)。

数週間から数か月以内での呼吸器症状や画像所見、上記に挙げた検査項目の増悪が認められた場合は、副腎皮質ステロイド大量療法(プレドニゾロン1mg/体重kg/dayの内服、もしくはメチルプレドニゾロンパルス療法の後、プレドニゾロン1mg/体重kg/dayの内服)を速やかに開始し、同時にカルシニューリン阻害薬の併用を行う(16-24)（エビデンスレベルIII-V)。シクロスポリンの場合は血中トラフ値を100-150 ng/ml程度に(17, 21, 23)、タクロリムスの場合は5-10ng/ml程度に(19)保つようにし、腎機能障害に留意しながら使用する（エビデンスレベルIII-V)。また、シクロホスファミドの間歇静注療法（エビデンスレベルIII-V）(19, 21, 24, 25)や免疫グロブリンの大量静注療法の併用(22, 26)（エビデンスレベルV）も重篤例や難治例に試みられる。CADMに伴う急速進行性IPには副腎皮質ステロイド大量療法とシクロホスファミド間歇静注療法およびシクロスポリンの併用が有効であったとする報告もある(23, 24)（エビデンスレベルIV-V)。なお、シクロスポリンや免疫グロブリン使用に対する保険適用はない。

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CQ20　心筋障害が合併する場合の治療法は何か

推奨文：高用量やパルス療法を含む副腎皮質ステロイド、免疫抑制薬を含む治療が行われる。(推奨度C1)

解説:症候性の心筋障害合併は約10-30%に認められ、その内訳として心不全、不整脈、心筋炎、冠動脈疾患が挙げられる(1, 2)。検査異常のみを呈する無症候性心筋障害例はより頻度が高い。症候性心筋障害合併例は非合併例と比較して生命予後が不良であるが(3)、治療法に関する十分なエビデンスはなく、筋炎重症例に準じ、以下の様な治療が行われている。

ステロイドパルス療法
高用量副腎皮質ステロイド
推奨度：C1
心筋障害合併例での治療反応性が詳細に追跡可能であった症例は10例(4-9)であった。このうち、8例(5-9)では免疫抑制薬により心筋障害が改善したと評価された。2例(5)では、免疫抑制薬開始後の経過中に新たに症候性の心筋障害を呈し、ペースメーカー挿入などの処置を要した。
免疫抑制薬が奏功した8例のうち、治療開始時にステロイドパルス療法を施行したのは7例(4, 6-8)、高用量副腎皮質ステロイド（1 mg/体重kg/day）を使用したのは1例(9)であった。病勢のコントロールが不良であった症例で致死的な心筋障害が顕在化した報告があることから、早期の疾患活動性沈静化が心筋障害に対しても有効であると推測される。この

ことから、心筋障害合併例については、ステロイドパルス療法、高用量副腎皮質ステロイドでの治療開始が考慮される（エビデンスレベルⅤ）。ただし、重症の心不全がある場合には、鉱質コルチコイド作用により心不全が増悪する可能性があるため、投与量の設定に注意を払うとともに、投与速度を減じるなど慎重な対応が必要である。

免疫抑制薬併用
推奨度：C1
解説：上記10例の報告ではいずれも初期から治療経過を通して免疫抑制薬が併用されていたが（のべ数：IVCY 4例(4, 7)、MTX 5 例(5,6, 8,9)、アザチオプリン4例(4)、 シクロスポリン 1例(7)、ヒドロキシクロロキン1例(4)、リツキシマブ1例(8))、このうち、4例(5, 7, 8)では初期からの免疫抑制薬併用にも関わらず治療抵抗性を示した。2例(7,8)は薬剤の変更により治療が奏功した。心筋障害が副腎皮質ステロイド抵抗性であることを示した根拠はないものの、予後不良な臓器障害に対する初期からの免疫抑制薬の併用は考慮される（エビデンスレベルⅤ）。なお、複数の免疫抑制薬について有効性を比較検討したエビデンスはないため、免疫抑制薬の選択については根拠のある推奨はない。
免疫グロブリン大量静注療法(6)、血漿交換療法(7)についてはともに1例ずつの使用例があるが、有効性を判断するには十分でない。

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CQ21 皮膚症状のみのDM患者や皮膚症状のみが遷延したDM患者の治療法は何か

推奨文：皮膚症状のみに対しては、経過観察またはステロイド外用による局所治療を行ってもよい（推奨度C1）

解説:皮膚症状のみを呈するDM(無筋症性皮膚筋炎、ADM）において筋症状や間質性肺炎が続発することがあるが、その間隔は個々の症例ごとに様々であり、数ヶ月から数十年以上にまでわたる。したがって、皮膚症状のみのDMでも慎重に経過観察する必要がある。また、ADMにおける悪性腫瘍合併の頻度は、古典的なDMと比して同等であるという報告もあり(1, 2)（エビデンスレベルIVb)、悪性腫瘍の検索も怠ってはならない。しかしながら、ADMに対して積極的にステロイドや免疫抑制薬を全身投与することは海外でも推奨されておらず、経過観察あるいは局所療法が主体となる(3, 4)(エビデンスレベルVI)。局所療法の有用性に関するRCTは存在しない。
　また、DM患者において、筋症状や全身的合併症が軽快したにもかかわらず皮膚症状のみが遷延することもしばしば経験される(5)(エビデンスレベルVI)。このような場合、残存する皮膚症状は、筋症状や全身的合併症の病勢が完全に抑制されていないということを意味するわけではない。したがって、ステロイドや免疫抑制薬の全身投与をさらに増量・追加することは一般には推奨されず、軽症の場合には経過観察するか、局所療法が治療手段の主体となる(6)(エビデンスレベルVI)。すなわち、ADMと同様の治療方針をとるべきである。

局所療法として最も一般的なのはステロイド外用薬である(6, 7)(エビデンスレベルVI)。顔面ではmildクラスを用い、体幹・四肢では通常very strongクラス以上が必要となるが、ステロイド外用で十分な効果を得ることは難しいことが多い。さらに、長期にわたる外用は皮膚萎縮や血管拡張などの副作用が生じる恐れがあるため、漫然と使用することは好ましくない。

DMの皮膚症状に対する局所療法としては、タクロリムス軟膏の有用性がオープン試験および症例報告により示されているが(8-10)(エビデンスレベルV)、無効であったとする報告もある(11)(エビデンスレベルV)。

DMではループスと同等の光線過敏症が報告されており(12)（エビデンスレベルIII)、顔面や前頚部などに日光裸露部紅斑を有する場合は、念のため日光暴露に注意してサンスクリーンの使用を促す。

掻痒に対しては抗ヒスタミン薬内服も行われる(6, 7)(エビデンスレベルVI)。

推奨文：著しい皮膚症状が存在する場合には、ダプソン（C1)、ガンマグロブリン静注療法（C1)、メトトレキサート（C1)、ミコフェノレートモフェチル（C1)、シクロスポリンA（C1)、あるいはタクロリムス（C1）による全身的な治療を考慮してもよい

解説：皮膚症状が広範囲に及び、患者のQOLを著しく障害する場合には、遷延した皮膚症状に対して全身的な治療を考慮してもよい（保険適用外）(6, 7)(エビデンスレベルVI)。全身療法に対するRCTで有用性が示されているものはない。

ダプソン（DDS）の内服が有用であったとする症例報告がある(13-15)(エビデンスレベルV)。また、海外ではヒドロキシクロロキンも使用されている(6)(エビデンスレベルVI)。

免疫グロブリン大量静注療法(IVIg)の有用性は、クロスオーバー試験において示されている(16)(エビデンスレベルII)。この試験では、12例のDM患者のうち8例で皮膚症状の著明な改善が認められた。このほかに、IVIgの有用性を示す症例報告がある(17-19)(エビデンスレベルV)。

免疫抑制薬では、MTXの有用性は、症例集積研究により報告されている(20-22)(エビデンスレベルV)。また、ミコフェノレートモフェチルの有用性も、症例集積研究により報告されている(23, 24)(エビデンスレベルV)。シクロスポリンAおよびタクロリムスはDMの皮膚病変への有用性が症例報告により示されている(25-27)(エビデンスレベルV)。これらの薬剤の使用にあたっては、副作用の発現の可能性に十分注意する必要がある。

生物学的製剤では、リツキシマブのパイロット研究で皮膚症状に有用であったとする報告(28)(エビデンスレベルIII)と限定的な効果しか認められなかったとする報告(29)(エビデンスレベルIII)がある。TNF阻害薬では、エタネルセプトとプレドニゾン併用のランダム化比較試験で、皮膚病変の改善はみられたものの、有意差はなかった(30)(エビデンスレベルII)。これらの生物学的製剤は強力な免疫抑制作用があり、その適応は慎重に考慮する必要がある。なお、TNF阻害薬によりDMが誘発されたとする報告があることにも注意が必要である。

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CQ22 DM 患者の石灰沈着に対する治療方法は何か

推奨文：標準的治療の後に残存する石灰沈着に対しては、低用量ワルファリン、塩酸ジルチアゼム、水酸化アルミニウム、ビスホスフォネート、プロベネシド、ガンマグロブリンの投与や外科的治療を考慮する（推奨度 C1）

解説：石灰沈着は、筋症状や全身症状の軽快後にも残存したり増悪したりすることのある皮膚症状である。小児 DM で特に多い。石灰沈着の治療には、低用量ワルファリン(1, 2)(エビデンスレベル II)、塩酸ジルチアゼム(3-5)(エビデンスレベル V)、水酸化アルミニウム(6)(エビデンスレベル V)、ビスホスフォネート(7-9)(エビデンスレベル V)、プロベネシド(10, 11)(エビデンスレベル V)、ガンマグロブリン静注療法(12, 13)(エビデンスレベル V)の有用性が報告さ

れているが、いずれも強い効果はない。外科的治療も考慮してよい(14)(エビデンスレベルV)。

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CQ23 悪性腫瘍合併筋炎では、悪性腫瘍の治療とともに筋炎に対する治療を行うべきか

推奨文：PM/DM の治療を待てる場合は、悪性腫瘍の治療をまず試みてよい。（推奨度Ｃ１）

解説：悪性腫瘍合併筋炎では基本的に悪性腫瘍と筋炎の両者の治療が必要であるが、悪性腫瘍に対する外科手術・化学療法と平行しての筋炎に対する副腎皮質ステロイド・免疫抑制薬の投与は創傷治癒の遅延や過度の免疫抑制を引き起こすという意見もあるため、どちらかの治療を優先したい場合も経験上多い。
悪性腫瘍合併筋炎についての症例報告は多数存在するものの、治療のプロトコールやタイミングについてのエビデンスの高い研究には乏しい。多数例の検討では 45 例中 8 例あるいは 13 例中 8 例と報告により差があるものの悪性腫瘍の進展と筋炎の病勢に相関がみられる症例は存在し(1,2) （エビデンスレベルV)、腫瘍の治療後 1 ヶ月で CK や LDH が有意に改善したという調査があり(3) (エビデンスレベルV)、腫瘍の治療のみで副腎皮質ステロイドを使用せずに筋炎が寛解した例も存在する(4-7) （エビデンスレベルV)。一方で、悪性腫瘍が未治療のうちに筋炎の治療を開始した場合、筋炎の治療反応性が悪く腫瘍の治療により反応性が増したと考えられる症例が報告されていること(8,9) （エビデンスレベルV)、後日手術・化学療法の際に副腎皮質ステロイドによる創傷治癒遅延・感染症の影響を検討する必要がでてくること、免疫抑制薬が悪性腫瘍の進展に影響を与える可能性などが考えられる。
以上を考え合わせると、PM/DM の治療を待てる場合はその前に悪性腫瘍の治療を検討べき症例が多いと思われる。上述の検討のように、悪性腫瘍治療後も筋炎が軽快しない場合もしばしば経験されるが、そ

の際は筋炎に対する治療を追加する。
一方、高度な筋炎・嚥下機能障害・呼吸筋障害あるいは間質性肺炎などが存在し経過観察が難しいと判断される場合は悪性腫瘍が未治療あるいは治療途中であっても、リスクについて検討した上でそれらの治療を開始する。

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別添２　多発（性）筋炎・皮膚筋炎治療ガイドライン（英語版）

Guideline for treatment of polymyositis and dermatomyositis approved by Japan College of Rheumatology, Japanese Society of Neurology, and Japanese Society of Dermatology.

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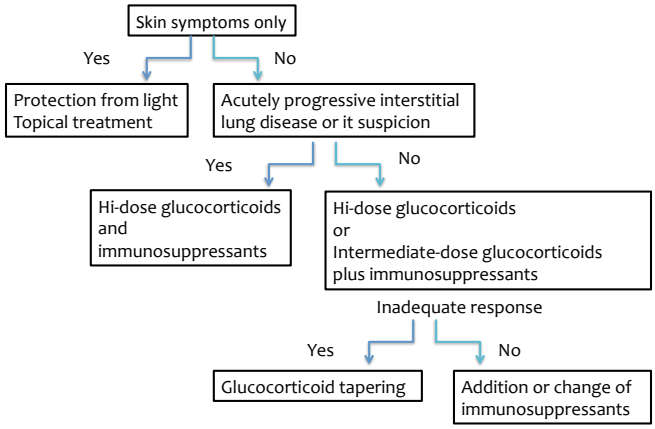
This guideline was established in accordance with Minds 2007 by the research team supported by the Ministry of Health, Labour and Welfare, Japan. Rheumatologists, neurologists, and dermatologists participated.
The treatment plan recommended as the first-line treatment is depicted in the figure.



Specific clinical questions asked were as follows.

CQ1. What are the clinical signs and laboratory tests that predict functional prognosis and therapeutic response? (Mimori)
CQ2. Are autoantibodies useful markers of myositis? (Mimori)
CQ3. Which is the best marker to trace clinical activity of myositis, CK or MMT? (Kanda)
CQ4. What is the first-line treatment for polymyositis and dermatomyositis? (Sunada)
CQ5. What is the validated initial dose of glucocorticoids? (Kohsaka)
CQ6. Can atrophied muscle recover with corticosteroid treatment? (Sunada)
CQ7. Is it possible to discontinue the corticosteroids after remission? (Fujimoto)
CQ8. How to distinguish between muscle weakness induced by PM/DM and by steroid myopathy? (Sunada)
CQ9. Which patients should you treat by the use of immunosuppressant with simultaneous prednisolone?

(Kawaguchi)
CQ10 Can Corticosteroid be tapered earlier by the addition of immunosuppressants? (Jinnin)
CQ11. Which immunosuppressants except corticosteroids can be effective for the treatment of PM/DM? (Kawaguchi)
CQ12. Can intravenous injection of immunoglobulins be a recommended treatment regimen in steroid-resistant PM/DM? (Kanda)
CQ13. What are the reliable markers for relapse of myositis that requires intensification of treatment? (Kohsaka)
CQ14. Which treatment should be selected in relapse of myositis? (Kohsaka)
CQ15. Should we take any measures to prevent opportunistic infections in patients with myositis-associated interstitial lung disease treated with GC and/or immunosuppressants? (Muro)
CQ16. Is rehabilitation during the early stage of treatment effective? (Sunada)
CQ17. Will muscle weakness in chronic stage myositis patients improve with rehabilitation? (Sunada)
CQ18. How should myositis patients with dysphagia be treated? (Kanda)
CQ19. How should myositis patients with interstitial lung disease be treated? (Muro)
CQ20. How should myositis patients with cardiac involvement be treated? (Kohsaka)
CQ21. How should DM patients only exhibiting skin manifestations or carrying only skin symptoms after treatment be treated? (Fujimoto)
CQ22. How should DM patients with skin calcification be treated? (Fujimoto)
CQ23. Should myositis and malignancy be treated simultaneously in patients with PM/DM and associated-malignancy? (Jinnin)

CQ1. What are the clinical signs and laboratory tests that predict functional prognosis and therapeutic response?

Recommendation: Some clinical symptoms/signs and laboratory tests can predict life prognosis and responsiveness to treatment (Recommendation Grade: C1)

Although it is difficult to predict precisely the prognosis and therapeutic response in myositis patients, some factors that correlate to the prognosis and therapeutic response have been known empirically.
The risk factors in life prognosis are old age [1,2], male sex [3], race (non-Caucasian) [3,4], period from development of symptoms to initiation of treatment [5,6], clinical subsets (cancer-associated myositis and clinically amyopathic dermatomyositis [DM]) [5,7], skin ulcer [7], dysphagia [4,8], respiratory complications (respiratory muscle weakness or interstitial pneumonia) [8-10], and cardiac involvement [8] (evidence level III-IV).

When muscle weakness is severe, dysphagia is an important sign of resistance to therapy and a risk factor regulating life prognosis [4,8]. In cancer-associated myositis, it has been reported that therapeutic responsiveness is usually poor. In limited patients, surgical resection of malignancy can improve the disease.

There is no consensus on correlation between serum CK levels and therapeutic responsiveness. When CK level is very high, it may be possible to predict that the patients should respond poorly to the treatment. Perhaps, it is merely because it should take long until the CK level becomes normal.

It has been reported that therapeutic responsiveness is poor when severe muscle fiber necrosis and poor inflammatory cell infiltration are found in muscle biopsy. This pathological features are related to presence of this anti-SRP antibodies.

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CQ2. Are autoantibodies useful markers of myositis?

Recommendation: Myositis-specific autoantibodies (MSA) and myositis-associated autoantibodies (MAA) are closely associated with clinical subsets, pathogenesis, clinical course and therapeutic responsiveness of patients with myositis. Therefore, it is recommended highly to measure anti-ARS antibodies including anti-Jo-1 and other specific autoantibodies. (Recommendation Grade: A)

Most of MSA and MAA should be useful in predicting the responsiveness to treatment for myositis and extra-muscular complications.

Among the autoantibodies, anti-Mi-2, anti-U1RNP and anti-Ku antibodies have been reported to predict relatively good response to glucocorticoids and good life prognosis, although the latter two antibodies are found in overlap syndrome [1-7] (evidence level IV).

Anti-Jo-1 and anti-aminoacyl-tRNA synthetases (ARS) antibodies (including anti-PL-7, anti-PL-12, anti-EJ, anti-OJ and anti-KS) are associated closely with interstitial lung disease (ILD) as well as myositis in the "anti-synthetase syndrome". Myopathy as well as ILD in anti-ARS-positive patients are resistant to GC therapy in general, whereas there is a report to suggest that they respond well to the initial therapy but suffer from frequent recurrence. The prognosis of respiratory function is poor when patients suffer from frequent recurrence of ILD. Therefore, the concomitant use of immunosuppressive drugs is recommended to prevent recurrence of the anti-synthase syndrome [8-10] (evidence level IV).

Although all anti-ARS antibodies accompany the same clinical manifestations, known as anti-synthetase syndrome, it has been reported that there are some differences in clinical features, course and prognosis among the patients with different anti-ARS antibodies. Frequency of myositis is higher in patients with anti-Jo-1 antibody, whereas lower in those with anti-PL-7, anti-PL-12 and anti-KS antibodies. On the other hand, frequency of ILD is higher in patients with anti-PL-7, anti-PL-12, anti-KS and anti-OJ than in anti-Jo-1-positive patients. Although prognosis is poorer in anti-PL-7 and PL-12-positive patients than in anti-Jo-1 positive patients, this may be due to delayed diagnosis in anti-PL-7 and PL-12-positive patients [8,11] (evidence level IV).

Anti-SRP antibody has been reported as a marker of severe, treatment- resistant and/or recurrent myositis. Patients with anti-SRP antibodies often have necrotizing myopathy, which is characterized by marked muscular fiber necrosis and poor inflammatory cell infiltration in the muscle biopsy specimen. Anti-SRP-positive myopathy is often resistant to GC therapy, and therefore needs immunosuppressive drugs and intravenous immunoglobulin from early stage of the disease [12,13] (evidence level IV). In recent years, effectiveness of rituximab has been reported in anti-SRP-positive and treatment-resistant myopathy patients [14] (evidence level V).

Anti-TIF-1γ/α (p155/140) antibody can be detected in DM patients, and more frequently in malignancy-associated DM patients. Therefore, intensive search of malignancies and careful follow-up are recommended in the patients with this antibody [7] (evidence level IV).

Anti-MDA5 (CADM-140) antibody is specific to clinically amyopathic dermatomyositis (CADM) and associated frequently with rapidly progressive ILD with poor prognosis [15,16] (evidence level IV). It is recommended to treat the patients with concomitant immunosuppressive drugs as well as high dose GC from the early stage of the disease when this autoantibody is positive or even suspected [17] (evidence level V).

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CQ3. Which is the best marker to trace clinical activity of myositis, CK or MMT?

Answer: Both CK and MMT are equally valuable in the clinical evaluation of myositis activity. (Recommendation Grade:B)

Maillard et al. assessed measures of muscle inflammation including muscle strength (manual muscle testing [MMT] and myometry) and function (Childhood Myositis Assessment Scale [CMAS], Children Health Assessment Questionnaire [C-HAQ]), the muscle enzymes LDH and CK, and T2-weighted MRI scans of the thigh muscles, in 10 children with active juvenile dermatomyositis (JDM), 10 with inactive JDM, and 20 healthy children [1]. The MRI T2 relaxation times were increased in active JDM compared with inactive JDM and healthy children, indicating a detectable increase in inflammation within the muscles. There was also good correlation between the MRI scores and the measures of muscle strength and function. However, there was no correlation between the MRI and muscle enzymes (Class IVb). In a case series of 19 JDM patients, signal intensity of muscle in T2-weighted image correlates with muscle strength assessment while abnormal MRI findings and serum levels of muscle enzymes (AST, CK and aldolase) have different sensitivities [2] (Class V).
Twenty-nine experts in the assessment of myositis achieved consensus on 102 adult and 102 juvenile paper patient profiles as for clinical improvement. Based on validity, discrimination power, reliability and ease to use, six core measures were shown: 1. physician's global assessment, 2. patient's/parent's global activity, 3. MMT, 4. physical function (HAQ/C-HAQ, CMAS), 5. muscle enzymes (CK, LDH, AST, ALT, Aldolase), and 6. extramuscular activity assessment. The definition of improvement (common to the adult and the pediatric working groups) that ranked highest was 3 of any 6 of the core set measures improved by $\geqq$20%, with no more than 2 worse by $\geqq$25% (which could not include manual muscle testing to assess strength [3]) (Class VI).
Most of the myositis experts agreed that MMT and CK are equally important in the clinical evaluation of PM/DM patients. Engel and Hohlfeld stressed the importance to monitor both the patient's strength by MMT and the serum CK. However, they also stated the importance of CK, because in patients responding to therapy, the serum CK decreases before the weakness; in those relapsing, the serum CK rises before the weakness recurs [4] (Class VI). On the other hand, Dalakas and Hohlfeld stated that the goals of therapy are to improve the ability to carry out activities of daily living by increasing muscle strength and to ameliorate

extramuscular manifestations (rash, dysphagia, dyspnea, arthralgia, fever). When improvement of the strength improves, the serum CK concentration falls concurrently. However, the reverse is not always true because treatments (eg, plasmapheresis) can lower the serum CK concentration without improving strength. This effect has been misinterpreted as "chemical improvement", and has formed the basis for the common habit of "chasing" or "treating" the CK concentration instead of the muscle weakness [5] (Class VI). In 2012 Cochran Review for immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis [6], only two outcome measures were accepted: 1. Change in a function or disability scale after at least six months, and 2. A 15% or greater improvement in muscle strength compared with baseline after at least six months (Class VI).

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CQ4. What is the first-line treatment for polymyositis (PM) and dermatomyositis?

In case with interstitial pneumonitis → CQ19
In case with malignancy → CQ25

Recommendation: The first-line treatment for PM/DM is administration of corticosteroids (Recommendation Grade: B).

Comments: As the first-line treatment for myositis, many experts recommend administration of prednisolone. In actual clinical practice, except for the associated difficulties, prednisolone is the treatment of choice in most cases. However, the use of prednisolone as the first-line treatment is based on empirical data without prospective or randomized clinical trials that assessed its efficacy [1-4] (evidence level VI).
In Japan, several corticosteroids are available for oral and intravenous administration. Although their potential differences in the efficacy have not been studied, methylprednisolone is used for steroid pulse therapy.
In juvenile DM, early treatment with combination corticosteroids and methotrexate is effective in an early reduction of corticosteroids [5,6] (evidence level V). In addition, it has been reported that the combination of methylprednisolone pulse therapy with oral corticosteroids had a higher improvement rate and significantly shorter time to normalize the creatine kinase (CK) level than oral corticosteroids alone [7] (evidence level III).
Different pathological mechanisms are proposed for specific PM/DM patient groups. Specific conditions impacting corticosteroid efficacy include old age, failure of organs other than muscle (e.g., interstitial pneumonia and/or malignant tumor complications) [1-4] (evidence level VI), and anti-signal recognition particle antibody positivity [8,9] (evidence level V). Future studies are required to determine the first-line therapy of individual patients and patient groups.

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CQ5. What is the validated initial dose of glucocorticoids?

Recommendation: Prednisolone 0.75-1mg/kg/day has been used for remission induction of PM/DM. (Recommendation Grade: C1)

High-dose glucocorticoids (GCs) has been used according to recommendations of specialists for lack of randomized controlled trials to investigate the initial dose of GCs. However, use of the lower dose of GCs become prevalent with increased use of concomitant immunosuppressants. Actually, a retrospective study that compared 15 patients treated with high-dose prednisolone (>0.5mg/kg/day, generally 1mg/kg/day) and 10 patients treated with low-dose prednisolone (=< 0.5mg/kg/day) and immunosuppressants disclosed that muscle enzymes and muscle functions after the treatment were comparable between the two groups [1)]. Vertebral fractures were less common in the low-dose group. Although muscle strength before the treatment and involvement of steroid myopathy were unclear, this study suggested that prednisolone less than 0.5mg/kg/day should be sufficient to treat PM/DM when immunosuppressants are used concomitantly.
There is no evidence as for the timing to start tapering GCs. Conventionally, the initial dose is maintained for 2 to 4 weeks and is tapered by 5 to 10mg/week according to the improvement of disease to avoid steroid myopathy. In general, it is easier to taper GCs when GC therapy is started with immunosuppressants [2)].
Usually, GCs are administrated daily in 3 divided doses. Alternatively, they can be administrated on alternate days or once every morning to avoid adrenal suppression. Even in such regimens, however, it is difficult to avoid adrenal suppression when the moderate or high dose of GCs is administered. The therapeutic effect is slightly reduced compared with daily administration in divided doses. Once-every-morning or alternate-day regimen may be considered when GCs are tapered to the low doses.

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CQ6. Can the atrophied muscles recover with corticosteroid treatment?

Answer: Atrophied muscle is expected to recover with the treatment.

Comments: Skeletal muscle mass is regulated by the balance between synthesis (anabolism) and degradation (catabolism) of the proteins constituting the skeletal muscle fibers. Several signals such as hormones, nutrients, cytokines, and physical tension are involved in adjusting this balance [1)] (evidence level VI).
The mechanism of muscle recovery through corticosteroid administration in myositis patients involves suppression of the muscle fiber damage accompanying inflammation, which is advantageous for muscle regeneration [2,3)] (evidence level VI). Conversely, corticosteroids induce skeletal muscle catabolism [4)] (evidence level IV). No report is available that studied the change in muscle mass during corticosteroid treatment in myositis patients. Although atrophied muscle is expected to recover, this is not supported with a high level of evidence.

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CQ7. Is it possible to discontinue the corticosteroids after remission?

Answer: Although no evidence is available whether the relapse rate is higher or not in the patients after corticosteroid discontinuation than those in continuing maintenance therapy, it is possible to discontinue corticosteroids in some cases.

Comments: Complete remission rate after the termination of medication has been reported to vary from 25% to 87% in PM/DM [1,2]. Various factors, including the disease type and the initial treatment, may affect the rate. Mostly, the reported remission rates were 40-60%, indicating that it should be possible to terminate the corticosteroids in some patients.

Phillips et al. reported that, in a retrospective study of 23 DM, 9 PM and 18 overlap syndrome patients (evidence level IVb), relapses occurred in 67% of PM, 65% of DM, and 50% of the overlap. Multiple relapses occurred in 60% in the DM group, 67% in the overlap group and 33% in the PM group [3]. In each of the three groups the greatest number of relapses occurred during maintenance therapy (46% in PM, 38% in DM, 77% in overlap). A significant number of relapses occurred in patients who had been off treatment (23% in PM, 18% in DM, 5% in overlap).

Marie et al. conducted a retrospective study of 77 PM/DM patients with a minimal follow-up duration of 18 months (patients who died before 18-month follow-up were included) [4]. They reported that 40% went into remission; 18% had monocyclic course and 64% had chronic continuous course. Recurrence occurred in 58%; 27% occurred during the tapering period of high-dose steroids or stable maintenance treatment, 19% during the tapering period of low-dose steroids, and 12% during off treatment (evidence level IVb).

Apparently, the disease relapses in some patients even if they are under continuing low-dose corticosteroids. However, it is impossible to compare directly the relapse rate of the group that terminated the therapy with that of the group that continued maintenance dose in PM/DM.

Bronner et al. reported long-term outcome in PM/DM, in which they re-examined 110 patients after a median follow-up of 5 years; 41% of the patients were still using corticosteroids and/or immunosuppressants. They identified anti-Jo-1 antibody positivity as a risk factor predicting the persistent use of drugs with a high odds ratio [5] (evidence level IVb). Thus, it is possible that patients with anti-synthetase syndrome, including anti-Jo-1 antibody, need treatment continuation more than other patients. Marie et al. assessed and compared long-term outcome between anti-synthetase syndrome patients with anti-Jo1 antibody and those with anti-PL7/PL12 antibody. In the anti-Jo-1 antibody-positive group and the anti-PL-7/PL-12 antibody-positive group, remission of myositis was observed in 21.3 and 46.2%, respectively [6]. The remission rates of interstitial lung disease were 29.4% and 5.6%, respectively. Therefore, the main targets of treatment may differ depending on the difference of the autoantibody profile.

At this moment, it is difficult to make a general classification of what types of patients need corticosteroid maintenance therapy. The decision of treatment continuation should be based on the clinical course of the individual patients.

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CQ8. How to distinguish between muscle weakness induced by PM/DM and by steroid myopathy?

Recommendation: A comprehensive approach with reference to the clinical and laboratory findings is used to distinguish between muscle weakness induced by PM/DM and by steroid myopathy.

Comments: Steroid myopathy is suspected when progressive muscle weakness occurs during long-term GC administration to treat myositis, with creatinine kinase (CK) values remaining normal or unchanged [1] (evidence level V), [2] (evidence level VI). However, in many cases, steroid myopathy occurs frequently with recurrence of the myositis. Also, concomitant systemic deterioration of the systemic conditions, such as disuse muscle atrophy, malnutrition and infection make differential diagnosis difficult.

The dose of GC and length of administration that induce steroid myopathy differ depending on the individual patients. In general, steroid myopathy is less likely when the patients take GC at the dose equivalent to 10 mg of prednisolone per day or less. The myopathy develops generally in two weeks after starting 40 - 60 mg per day. Administration for 1 month induced some degree of muscle weakness [3] (evidence level III). Patients with malignancy and the elder patients are also prone to the

steroid myopathy [4] (evidence level VI). Patients with steroid myopathy often develop other GC side effects, including a moon face, diabetes, central obesity, psychiatric changes, dermatological symptoms and osteoporosis [3] (evidence level III).

Steroid-induced muscle weakness occurs predominantly in the proximal muscles and occurs rarely in the distal muscles. Therefore, it tends to be more noticeable in the pelvic-girdle muscles than in the upper limbs [3] (evidence level III) [5] and (evidence level VI).

Needle electromyography should reveal myogenic changes but not spontaneous discharges. This finding is useful in differentiating steroid myopathy from myositis relapse [1] (evidence levels VI) [4] (evidence level V) [6] and (evidence level VI).

In steroid myopathy, 24-hour excretion of creatinine in the urine increases. This can serve as a diagnostic reference [1] (evidence level V), but not always helpful [3] (evidence level III).

Muscle pathology should disclose selective type 2 fiber atrophy [4] (evidence level VI) 7) , (evidence level IV) [8] (evidence level IV). Relapse is suspected when high signal intensity changes are seen on the fat-suppressed T2-weighted skeletal MRI scans [9] (evidence level VI) [10] (evidence level VI). However, the same findings can also be seen in muscles subjected to an excessive exercise load. MRI scan should be carried out after sufficient muscle rest of the patients.

When steroid myopathy is diagnosed, the clinical course of muscle strength, changes in CK levels, laboratory findings, and treatment content in the 2 months before the diagnosis should be taken into consideration [2] (evidence level VI). In some cases, the diagnosis can be made only by monitoring the muscle weakness 2–8 weeks after reducing the GC dose [2] (evidence level VI). Steroid myopathy improves 3–4 weeks after appropriate dose reduction of GC [3] (evidence level III).

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CQ9. Which patients should be treated with immunosuppressants together with concomitant glucocorticoids?

Recommendation: Immunosuppressants should be given to patients with PM/DM who are resistant to glucocorticoid (GC) therapy. (Recommendation Grade: B)

Patients with PM/DM can be treated with methotrexate (MTX), azathioprine (AZA), tacrolimus (Tac), and cyclosporine A (CsA) in combination with GC as the first line therapy. (Recommendation Grade: B)

Comments: Since the 1950s, the standard treatment of myositis has been administration of a high-dose GC [1]. It has been observed that some patients do not respond to GC alone. Other patients treated wuth GC alone experience recurrence after the dose of GC is tapered. In the article by van de Vlekkert et al. in 2010 [2], recurrence was observed in approximately 45% of cases treated with GC alone (evidence level II).

In short, many patients respond to the high-dose GC as an initial treatment and go into remission, but suffer from relapse during GC tapering. In the cases of relapse, the combination therapy with immunosuppressants should be selected [3].

However, long-term GC treatment can evoke steroid-induced muscle atrophy, making full recovery of the muscle strength difficult. Therefore, it is necessary to make treatment period with a high-dose GC as short as possible. On the other hand, it is necessary to consider the increase in the amount of GC for the cased of relapse.

Based on these facts, the initial treatment with GC together with methotrexate (MTX), azathioprine (AZA), tacrolimus (Tac) [4], or cyclosporineA (CsA) [5] should be effective and should reduce the rate of relapse during the GC tapering (evidence level VI).

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CQ10. Can glucocorticoids be tapered earlier when immunosuppressant is added?

Recommendation: The addition of immunosuppressants is useful for earlier tapering of the dosage of glucocorticoids (GC). (Recommendation Grade: C1)

Comments: Although no multicenter randomized control trails are available to answer the CQ, a randomized trial by Bunch et al., which compared the effects of prednisone plus azathioprine with those of prednisone alone in 16 patients provides highest evidence. In their observation after three years, patients treated with the combination therapy needed lesser doses of prednisone as maintenance therapy (1.6 mg/day versus 8.7 mg/day) as well as had better functional outcomes [1)] (evidence level II).

Furthermore, many case reports have indicated that the addition of immunosuppressants is useful for earlier tapering of GC. For example, Qushmaq et al. described that case series of 6 PM/DM (4 PM and 2 DM) refractory to GC therapies were treated by cyclosporin A of mean dose 3.5mg/kg/day for a median of 6 months, which resulted in the reduction of the dosage of GC by approximately 75% [2)] (evidence level V). In 14 juvenile DM patients who had not responded to GC and other immunosuppressants, the treatment with cyclosporin A led to the recovery of muscle strength and the reduction of GC [3)] (evidence level V).

Wilkes et al. reported that treatment of 13 patients of the antisynthetase syndrome and interstitial lung disease with tacrolimus for a mean duration of 51 months improved the muscle or lung involvement, and reduced the mean prednisone dose by 67% [4)] (evidence level V).

A retrospective review of 50 juvenile DM patients treated with mycophenolate mofetil indicated that the skin and muscle disease activity decreased and that GC dosages became lower after 12 months of the therapy [5)] (evidence level V). In addition, mycophenolate mofetil treatment in 12 DM patients who had the skin lesions recalcitrant to traditional therapies or who developed toxic effects from traditional therapies decreased the dosage of GC by 93% [6)] (evidence level V). Also, in 10 DM patients treated with mycophenolate mofetil in combination with GC, successful GC taper was achieved in six patients [7)] (evidence level V).

Thirty-one juvenile DM patients treated with methotrexate and GC had a shorter average time to discontinuation of prednisone and a lower average cumulative prednisone dose compared to 22 historical controls those who received only GC, although recovery of muscle strength and physical function were similar in both groups [8)] (evidence level V). In 13 DM patients, the addition of methotrexate allowed reduction or discontinuation of GC [9)] (evidence level V). Furthermore, the initial prednisone dose was halved after 13 weeks in amyopathic DM patients [10)] (evidence level V).

Taken together, these reports indicated various immunosuppressants make early tapering the GC doses as steroid-sparing agents, although the evidence levels of each report is not high.

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CQ11. Which immunosuppressants except glucocorticosteroids can be effective for the treatment of PM/DM?

Recommendation: Azathioprine, methotrexate, tacrolimus, cyclosporine A, mycophenolate mofetil, or cyclophosphamide can be effective. (Recommendation Grade: B)

Comments

1. Azathioprine (AZA)

Around 1980, the efficacy of combination therapy with GC was reported [1,2]. For juvenile DM, survival rates were improved using MTX or AZA as an initial therapy. AZA is considered an option at the time of myositis relapse.

Dose of 50-100 mg/day, min 1-2 administrations

2. Methotrexate (MTX)

The efficacy of MTX has been reported for myositis relapse [3,4]. In some clinical trials of juvenile DM, including one randomized controlled trial, the combination therapy of GC and MTX as initial treatment has been shown to be effective in the early GC tapering. MTX is considered an option at the time of myositis relapse. Although MTX is not covered officially by health insurance in Japan, it is expected to yield good results.

Daily dose to dose 7.5-15 mg / week

3. Tacrolimus (Tac)

The efficacy of Tac has been reported in myositis relapse [5-7]. The CK level, aldolase level, and MMT score were improved significantly in patients receiving GC and Tac combination therapy compared to those of patients receiving GC alone. Tac is also considered an effective drug at the time of myositis relapse. It has been shown to be effective for interstitial lung disease (ILD) in PM/DM and myositis unresponsive to CsA. Japanese insurance covers interstitial pneumonia treatment associated with PM / DM.

Two-minute administration to reach the optimal dose with trough concentration of 5-10 ng / ml

4. Cyclosporin A (CsA)

A randomized controlled trial showed CsA to be effective in the early GC tapering [8]. CsA is an option at the time of myositis relapse. In patients with PM/DM and associated ILD, combination therapy of CsA and GC improved the prognosis of ILD more effectively than GC alone [9,10].

Two-minute administration to reach the optimal dose trough concentration of 100-150 ng / ml

A method for distributing 1 dose to reach a 2-hour value of 1,000 ng / ml may also be used.

5. Mycophenolate mofetil (MMF)

The efficacy of MMF has been reported for myositis relapse [11-13]. In a cohort of 50 patients with juvenile DM, the activity index of dermatitis and myositis was improved significantly by the administration of MMF [13]. Therefore, MMF is considered an option at the time of myositis relapse.

Dose of 1-3 g / day, 2-minute administration

6. Cyclophosphamide (CPA)

CPA is administered for PM/DM less often than for other connective tissue diseases. However, CPA was reported to be effective as a surrogate for CsA in the treatment of recurrent myositis and was used to treat ILD with PM/DM [14]. Therefore, it could be used in the treatment of refractory myositis and myositis relapse.

A dose of 50-100 mg / day, with a minimum of 1-2 administrations through intravenous infusion for a 500 mg/m2 of body surface area every four weeks.

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CQ12. Can intravenous injection of immunoglobulins (IVIg) be a recommended treatment regimen in steroid-resistant PM/DM?

Recommendation: IVIg treatment can be initiated in steroid-resistant DM (Recommendation Grade: B) and PM (Recommendation Grade: C1) patients.

Two randomized clinical trials were reported [1,2]. Dalakas et al. conducted a double-blind, placebo-controlled study of 15 patients (age, 18 to 55 years) with biopsy-proved [3], treatment-resistant DM. The patients continued to receive prednisone and were randomly assigned to one infusion of immune globulin (2 g per kilogram of body weight) or placebo per month for three months, with the option of crossing over to the alternative therapy for three months. The eight patients assigned to immunoglobulins had a significant improvement in scores of muscle strength ($P<0.018$) and neuromuscular symptoms ($P<0.035$), whereas the seven patients assigned to placebo did not. Repeated biopsies in five patients of muscle whose strength improved to almost normal also showed improvement [1] (Class II).
Miyasaka et al. conducted a randomized, double-blind, placebo-controlled study of 16 steroid-refractory patients (16 PM and 10 DM, based on Bohan and Peter criteria [4,5]). They were assigned randomly to receive IVIg or placebo, and the IVIg group showed significant improvement in the primary endpoint (MMT score) and the secondary endpoints (serum CK level and ADL score). However, placebo group also showed significant improvement. No significant difference was observed between two groups [2] (Class II).
A case-control study by Danieli et al. [6] enrolled 20 refractory patients (8 PM and 12 DM, based on Bohan and Peter criteria [4,5]) treated by prednisone and cyclosporine A. The patients were divided into three groups: no additional treatment (n=7), additional IVIg (1 g/kg body weight/day 2 days/month, for 12 months; n=7), additional IVIg plus plasmapheresis (n=6). Patients receiving prednisone and cyclosporine A plus IVIg had a significantly higher probability of maintaining complete remission at the end of the four year follow up period than those treated with prednisone and cyclosporine A alone ($P<0.001$). No further benefit was added by the plasmapheresis (Class IVb).
Several case-series and single case reports dealing with the therapeutic effect of IVIg have been published. Most of them described favorable effects of IVIg in the improvement of MRC score, serum CK level and ADL score. Some case-series also commented on the beneficial outcome of IVIg treatment for dysphagia [7,8] (Class V): the percentage of full-remission was from 38% [8] (Class V) to 100% (with oral mycofenolate mofetil [9] (Class V)).
According to the evidence-based guideline of IVIg in the treatment of neuromuscular disorders, committed by the American Academy of Neurology and published in 2012 [10], IVIg treatment for nonresponsive dermatomyositis in adults was ranked Level C (IVIg may be considered) (Class VI).

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CQ13. What are the reliable markers for relapse of myositis that requires intensification of treatment?

Recommendation: Muscle enzymes, such as creatine kinase (CK) and aldolase (ALD), and manual muscle testing are used as markers of disease activity. Image findings, visual analog scale and electromyography findings are also useful. As total evaluation with several markers is important, composite measures that integrate these markers are proposed to assess disease activity. (Recommendation Grade: B)

Comments:

Muscle enzymes (Recommendation Grade: B)

Although no validated definitions of the relapse are available, elevation of serum CK and ALD levels has been used as an indicator of relapse. In most clinical studies, their levels were measured to evaluate disease activity and to identify relapse of myositis or refractory diseases. In all the 26 studies published in the major journals between 1993 and 2012, serum CK and ALD levels were measured and considered as indicators of myositis relapse [1-26].

Manual Muscle Testing (MMT) (Recommendation Grade: B)

Although no validated definitions of relapse are available, deterioration of MMT scores has been used as an indicator of relapse. In most clinical studies, MMT was assessed to evaluate disease activity and to identify relapse of myositis or refractory diseases. In 23 out of the 26 studies published in the major journals between 1993 and 2012, MMT scores were considered as an indicator of myositis relapse [4-7,9-26]. Although the MMT scores are good markers in considering intensification of treatment, clinicians should rule out muscle weakness attributable to steroid-induced myopathy.

Magnetic resonance imaging (MRI) (grade of recommendation C1)

Since correlation between the fat suppressive image signal intensity with short tau inversion recovery (STIR) and clinical disease activity was demonstrated in 1991 [27], the STIR image has been used as an indicator of the myositis relapse 28). A previous report showed that fat-corrected T2 measurement should be useful for assessing disease activity [28].

Visual analog scale (VAS) (Recommendation Grade: C1)

In patients with juvenile DM, the cutaneous assessment tool (CAT) activity score was highly correlated with physician's global assessments of disease activity measured with the 10-cm visual analog scale (VAS) [29]. VAS is listed as an assessment tool of disease activity and damage in the core set measures developed by International Myositis Assessment & Clinical Studies group (IMACS).

Electromyography (EMG) (Recommendation Grade: C1)

EMG is a useful tool for diagnosis of myositis [30]. A case report demonstrated that EMG was also useful for detecting relapse of myositis [31].

IMACS core set (Recommendation Grade: C1)

IMACS recommended that exacerbation of myositis should be defined in each clinical trial using the six parameters below [32].

1. physician global disease activity
2. parent/patient global disease activity
3. manual muscle strength testing (MMT)
4. physical function
5. laboratory measurements and 6. extramuscular disease

complications
Although the number of clinical trials that used the above parameters is still low, they will become common as a core set measures [33,34].

Functional index (FI) (Recommendation Grade: C1)
FI is a testing to evaluate muscle endurance in inflammatory myopathies by scoring the number of repetitions for tasks with a constant rhythm, and was reported by Josefson in 1996 [35]. Recently, the good correlation between Functional Index 2 (FI-2), which is a simplified version of FI, and physical function was demonstrated in patients with PM/DM [36]. Although FI has never been used as an index of myositis relapse, some clinical trials employed it for an outcome measure.

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CQ14. Which treatment should be selected in relapse of myositis?

Recommendation: Increase of GC to 0.5~1.0 mg prednisolone /kg body weight /day, or addition of immunosuppressants, IVIg, biological agents (tocilizumab, abatacept, rituximab, or TNF inhibitors), plasma pheresis have been the choice.

Increase of glucocorticoids (Recommendation Grade: B)
In the disease flare, dose escalation of GC to 0.5～1.0 mg prednisolone /kg body weight is recommended [1-3]. However, there are not enough data to recommend a specific dose of glucocorticoids. Concomitant use of immunosuppressive agents should be considered in the patients who will not tolerate adverse effects of the increased GC doses.

Immunosuppressants (Recommendation Grade: B)
（See CQ11 for details）

Intravenous immunoglobulin (IVIg) (Recommendation Grade: B)
Many studies demonstrated the efficacy of IVIg for relapse of PM/DM and refractory diseases [4-6]. IVIg reduced frequency of relapse significantly and improved long-term prognosis. It was effective for PM/DM patients with dysphagia or ILD [7,8]. Although repeated treatments are required for the long-term benefit, IVIg may be considered as one of the therapeutic agents for relapse of PM/DM.

Tocilizumab (Recommendation Grade: C1)
Recently, it was reported that two patients with refractory polymyositis responded well to tocilizumab. This fact suggested the efficacy of IL-6 blockade for relapse of PM/DM [9]. Although, the role of IL-6 in the pathogenesis of PM/DM is still unclear, IL-6 has been proposed as a biomarker of disease activity in DM [10].

Abatacept (Recommendation Grade: C1)
There are 2 reported cases of refractory and relapsing myositis responded well to abatacept [11,12]. Abatacept might be a beneficial option for the treatment of refractory myositis. Controlled trials are expected to demonstrate its efficacy.

Rituximab (No recommendation grade)
The efficacy of rituximab in PM/DM has been suggested by case reports and uncontrolled trials [13-17]. However, in the recent randomized controlled trial assessing its efficacy in 200 PM/DM patients, no differences were disclosed in response rates between the rituximab and placebo arms. Thus, it failed to show the efficacy of rituximab for refractory disease [18].

TNF inhibitors (Recommendation Grade: C2)
In a retrospective study, 6 of 8 patients with refractory PM/DM treated with TNF inhibitors showed a favorable response [19]. Subsequent trials failed to demonstrate the efficacy of the TNF inhibitors for refractory PM/DM [20,21]. Furthermore, rare but considerable cases of TNF inhibitor-induced PM/DM were reported [22,23]. Based on these facts, the TNF inhibitors are not recognized as a valid therapeutic agent for PM/DM.

Plasma pheresis (Recommendation Grade: C2)
Some case reports reported favorable outcomes after plasmapheresis for relapse of myositis [24]. However, a double blind, placebo-controlled trial failed to demonstrate the effectiveness of plasmapheresis and leukapheresis in chronic refractory PM/DM [25].

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CQ15. Should we take any measures to prevent opportunistic infections in patients with myositis-associated interstitial lung disease treated with GC and/or immunosuppressants?

Recommendation: When high-dose GC and/or immunosuppressants are administered to myositis patients with interstitial lung disease, measures should be taken to prevent opportunistic infections such as pneumocystis pneumonia (Recommendation Grade: A).

Comments: Opportunistic infections developed in 18 (11.5%) of 156 PM/DM cases in a French study [1)], and in 33 (11.8%) of 279 cases in another French study [2)] (evidence level IV). In the most cases, the pathogens were fungi, most commonly Candida albicans and Pneumocystis jiroveci. The peripheral blood lymphocyte count and the serum total protein concentration in the patients with opportunistic infections were lower than those in patients without opportunistic infections [1)]. In addition, neither adrenal GC nor immunosuppressant was used in 2 of the 18 patients with opportunistic infections while the other were treated with a various doses of GC. Seven patients took immunosuppressants together with GC.

In 75 patients with SLE or PM/DM under more than 40 mg/day of prednisolone, pneumocystis pneumonia arose as a complication in 7 cases (9.3%), who are all with interstitial lung disease [3)] (evidence level IV). No pneumocystis pneumonia develpoed in cases who were under the sulfamethoxazole-trimethoprim combination as prophylaxis (evidence level IV) [4)].

In 2011, the American Thoracic Society recommended use of one tablet/day of sulfamethoxazole-trimethoprim combination or two tablets for three days a week in patients under prednisone more than 20 mg/day for more than a month, particularly with an immunosuppressant [5)]. The same should be recommended to prevent pneumocystis pneumonia during treatment of the myositis-associated interstitial lung disease (evidence level VI).

Regarding the prevention of pulmonary tuberculosis, similar prevention should be considered to those for patients infected with HIV A prophylaxis, such as isoniazid administration, should be considered in patients with old lesions of pulmonary tuberculosis [6)] (evidence level VI).

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CQ16. Is rehabilitation during the early stage of treatment effective?

Recommendation: Beginning rehabilitation in the early stage of treatment has been reported as effective in muscle strength recovery. As it has not been reported to be harmful, rehabilitation may be implemented. However, the definitive prognosis of improvement in functions is unclear. Furthermore, the appropriate load for rehabilitation is currently not determined (Recommendation Grade: C1).

Comments: Except for several reports of small case series, randomized clinical trials or large-scale studies verifying the effects of early stage rehabilitation for the treatment of PM/DM, and its adverse events have not been conducted. Alexanderson et al. determined the effect of a 12-week-long resistive training on 11 patients in the early stage of PM/DM and reported recovery in both activities of daily living (ADL) and body functions without increasing the CK level (evidence level V) [1)].
In addition, Escalante et al. evaluated the effects of combination resistive and non-resistive exercises in four PM/DM subjects as well as the impact of resistive exercise alone on one subject [2)]. Manual muscle testing and ADL scores and peak isometric torque of lower limbs were evaluated. They indicated that three subjects in the first group experienced the effects of both exercises, whereas the remaining one subject experienced no effects. Improvement in the muscle strength was noted in one case receiving only resistive exercise. In addition, significant increase in the CK level was not observed after any of the exercises in any of the subjects in that study (evidence level V).
One major caveat with the abovementioned studies is the lack of a control group. Changes in functional prognosis based on the presence or absence of rehabilitation implementation are unclear. However, harm caused by rehabilitation has not been reported.
In addition, changes in functional prognosis based on the level of load have not been examined. Thus, the appropriate load for use in rehabilitation remains unclear.

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CQ17. Will muscle weakness in chronic stage myositis patients improve with rehabilitation?

Recommendation: Rehabilitation at chronic stage is probably effective in muscle strength recovery without aggravating inflammation and thus is recommended (Recommendation Grade: B).

Comments: Several small-scale randomized clinical trials investigated the outcomes of rehabilitation and adverse events in chronic stage PM/DM. Wiesinger et al. determined the effects of 6-week-long physical loads, such as cycling and stepping up and down a step tool, in 14 PM/DM patients and showed that the ADL score, muscle strength in the lower limbs, and peak oxygen consumption of muscle were markedly higher in the treatment group than in the control group without the exercise load [1)]. They observed no increase in the CK level or exacerbation of inflammation. In addition, Wiesinger et al. performed randomized clinical trials with an extended duration of 6 months and showed that both the muscle strength and ADL score improved without any adverse events [2)].
In addition, in a non-randomized clinical trial, Alexanderson et al. assessed the effect of exercise load on a group of chronic stage PM/DM patients and reported no aggravation of inflammation in the muscle biopsy specimens or increase of abnormal findings in muscle magnetic resonance imaging in patients with improved muscle strength and ADL score [3,4)].

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CQ18. How should myositis patients with dysphagia be treated?

Recommendation: IVIg is a recommended therapeutic option to treat steroid-resistant dysphagia. (Recommendation Grade: C1)

Although no RCTs or observational comparative studies were present concerning the treatment of dysphagia in PM/DM, two relatively large case-series were published [1, 2]. Marie et al. retrospectively reviewed the medical records of IVIg-treated 73 patients (39 with PM, 34 with DM, based on Bohan Peter criteria [3,4]) with steroid-resistant esophageal involvement 1). The median length of the patients' follow-up after institution of IVIg therapy (1gm/kg daily for 2 days each month: median 7 months of treatment) was 32 months and sixty patients (82.2%) exhibited resolution of their esophageal clinical manifestations (Class V). Four other patients (5.5%) improved but they still experienced mild dysphagia intermittently. Another patient successfully underwent cricopharyngeal myotomy. Eight patient died from aspiration pneumonia (n=6) and cancer (n=2).

Oh et al. retrospectively analyzed 62 patients with inflammatory myopathy-associated dysphagia seen at Mayo Clinic, Rochester between 1997 and 2001: 26 with IBM, 18 with DM, 9 with PM, and 9 with overlap syndrome (2) (diagnosis of PM/DM was based on Dalakas criteria [5]). Fifty-five patients (20 with IBM, 17 with DM, 9 with PM, and 9 with overlap syndrome) received immnosuppressive therapy including prednisone, azathioprine and methotrexate, and IVIg was administered in one with IBM, 4 with DM, 2 with PM, and 1 with overlap syndrome. Eleven patients reported resolution of their dysphagia (6 with DM, 4 with overlap syndrome, and 1 with PM). On the other hand, the patients with IBM had the least improvement; none had resolution of dysphagia. The improved outcome in IBM was noted only after cricopharyngeal myotomy (n=4) and dilation and reflux treatment (n=1) (Class V).

Palace et al. reported a 69-year-old woman with isolated dysphagia due to PM [6]. Her symptoms and signs were restricted to swallowing difficulties for 3 years and was successfully treated by oral prednisolone 40 mg daily (Class V). Other effective therapies described in case-series and single case reports are as follows: IVIg [7,8] (Class V), ciclosporine A [9] (Class V), intravenous cyclophosphamide plus oral methotrexate [10] (Class V), cricopharyngeal myotomy [11,12] (Class V), and endoscopic balloon dilatation [13] (Class V).

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CQ19. How should myositis patients with interstitial lung disease be treated?

Recommendation: Administration of high-dose GC (prednisolone 1mg/ body weight kg) is recommended. In the case with acutely progressive interstitial lung disease (ILD) and high risk patients, such as CADM patients,

immunosuppressants should be started together with GC. (Recommendation Grade: B)

Comments: It is reported that a half of PM/DM patients have ILD [1]. In planning treatments, both myositis and ILD are therapeutic targets we need to select from as a primary target. Although both are equally important in general, ILD is more important in patients in some subtypes of myositis. To predict the prognosis and treatment response of ILD, chest imaging (HRCT), pathological findings and autoantibody profiles should be evaluated as much as possible [1-6] (evidence level IV) (Recommendation Grade: B). ILD complicated with DM has worse prognosis than ILD complicated with PM [7-9] (evidence level IV).

High-dose GC therapy (prednisolone 1mg/ body weight kg/day) is effective for ILD complicated with PM/DM in many cases. Thus, as we do in the treatment of myositis, we can observe carefully the response of ILD to steroid monotherapy as initial treatment [1] (evidence level IV-V). However, intensive immunosuppressant treatment should be initiated together with high-dose GC treatment in some cases with ILD since they are often intractable or recurrent. This is especially true in the cases with rapidly progressive ILD complicated with CADM since they are particularly resistant to conventional treatments, and prone to death [1] (evidence level IV-V). The following are useful indicators of disease course and prognosis: PaO2/FiO2 ratio and A-aDO2 level 5, [10, 11], changes in KL-6 and SP-D [12], the presence of anti-MDA5 antibody and changes in its titer [11-15], and ferritin level and changes in its level [11] (evidence level IV-V).

When respiratory symptoms, image findings and/or the examinations listed above progress in less than several weeks or months, high-dose GC (oral administration of prednisolone 1mg/ body weight kg/day with or without methylprednisolone pulse therapy) together with calcineurin inhibitor should be started [16-23] (evidence level III-V). Blood trough level at 100-150 ng/ml for cyclosporine [17,21] and at 5-10 ng/ml for tacrolimus [19] should be maintained unless renal damage is noted (evidence level III-V). Addition of cyclophosphamide intermittent intravenous therapy [19,21,23,24] (evidence level III-V) and/or a high dose of intravenous immunoglobulin [22,25] (evidence level V) are tried for serious or intractable cases. There are reports that high-dose GC therapy in combination with intermittent cyclophosphamide intravenous therapy and cyclosporine was effective in treating rapidly progressive ILD with CADM [23] (evidence level IV).

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CQ20. How should myositis patients with cardiac involvement be treated?

Recommendation: High-dose glucocorticoids including three consecutive pulses of intravenous methylprednisolone in combination with immunosuppressive agents should be considered. (Recommendation Grade: C1)

Comments: Symptomatic cardiac complications have been reported in 10-30 % of patients with PM/DM, including congestive heart failure, arrhythmia, myocarditis and coronary disease [1,2]. More patients are diagnosed to have subclinical cardiac involvements with cardiac MRI or measurement of cardiac enzyme. Although cardiac involvement is a significant prognostic factor for death [3], no solid evidence for therapeutic options are available. Patients with cardiac involvement are treated accordingly as refractory cases.

Methyprednisolone pulse therapy and high-dose GC

Detailed therapeutic courses and the outcomes of 10 PM/DM patients with cardiac involvement were reported previously [4-9]. While 8 patients responded well to immunosuppressive agents, the other 2 patients developed new cardiac symptoms, which required pacemaker implantation even after treatment with immunosuppressants.
Among the above 8 cases, 7 patients were treated with three consecutive pulses of intravenous methylprednisolone 500-1000 mg/body followed by oral high-dose GC [4,6-8]. The other one case was treated with oral high-dose GC alone (1 mg predonisone /body weight kg) [9]. Administered GC doses in the 2 cases of treatment failure were not described. Because a patient, who did not respond to the initial treatment and remained to have active diseases, developed life-threatening cardiomyopathy, early control of disease activity should be important in treating PM/DM with cardiac involvement. Thus, pulse GC therapy followed by high-dose oral GC is recommended as the initial treatment (evidence level V). In cases with severe congestive-heart failure, reduction of dose and administration rate of intravenous methylprednisolone should be considered to avoid exacerbation of the heart failure by the mineral corticoid action of GC.

Immunosuppressants and other agents

Immunosuppressants were used from the early stage of treatment in all of the above 10 cases (cyclophosphamide; 4 cases [4,7)], methotrexate; 5 cases [5,6,8,9)], azathioprine; 4 cases [4)], cyclosporine; 1 case [7)], hydroxychloroquine; 1 case [4)], rituximab; 1 case [8)], in total number). Nonetheless, 4 cases were resistant [5,7,8)], and 2 cases improved only after two or more trials of immumosuppressive agents [7,8)]. Although there is no evidence that cardiomyopathy is resistant to GC, concomitant use of immunosuppressants from the initial stage of treatment should be considered to avoid poor prognosis (evidence level V). Solid recommendations for the choice of immunosuppressants are not established because of the lack of controlled clinical trials.

Alternatively, patients were treated intravenous injection of immunoglobulins [6)] and plasma exchange [7)]. Further investigations are required to confirm their efficacy.

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CQ21. How should DM patients only exhibiting skin manifestations or carrying only skin symptoms after treatment be treated?

Recommendation: Observation or topical corticosteroid therapy should be required for DM patients with cutaneous manifestation alone.

Comments:

DM patients with skin manifestations alone (patients with amyopathic DM [ADM]) may develop muscle diseases and/or interstitial lung diseases subsequently. The intervals between the onsets of skin and other manifestations vary depending on the individual cases, and range from months to decades. Therefore, careful follow-up is necessary even for DM patients with skin manifestations alone. Moreover, the ADM patients have malignancies as frequently as patients with classical DM [1,2)] (Evidence level IVb), and thus should be examined for presence of malignancies.

Systemic administration of GC or immunosuppressants to DM patients with skin manifestations alone is not recommended in our and foreign countries. Instead, observation or topical therapy is the standard care [3,4)] (evidence level VI). No RCT is available for the efficacy of topical therapy.

Occasionally, DM patients carry skin symptoms even after the treatment that resolves muscle and systemic symptoms successfully [5)] (evidence level VI). Thus, the remaining skin manifestations do not necessarily indicate persistent activities of muscle diseases and unsuppressed systemic complications. Therefore, further increase and/or addition of systemic administration of GC and/or immunosuppressive agents are generally not recommended. Observation or topical therapy should be considered again for such patients as is the case with ADM [6)] (evidence level VI).

GC are the most common agents for topoical therapy [6, 7)] (evidence level VI). Mild class GC should be applied for the facial lesions, while very strong class or upper class GC is required for the lesions in the trunk/extremities. Nonetheless, the treatment is often difficult. In addition, since the long-term use of topical GC can induce side effects including skin atrophy and telangiectasia, unnecessary use should be avoided.

Regarding other topical therapies, an open study and case reports have indicated the usefulness of tacrolimus ointment for the treatment of cutaneous symptoms of DM [8-10)] (evidence level V). However, there is a report showing that it was not effective [11)] (evidence level V).

Like lupus patients, DM patients exhibit photosensitivity [12)] (evidence level III). When the patients have erythematous lesions in the sun-exposed area such as the

face and the fore neck, the protection from light and the use of sunscreen should be encouraged.
Oral antihistamines are also used for pruritus [6,7] (evidence level VI).

For severe skin symptoms, systemic administration of dapsone (Recommendation Grade: C1), intravenous gamma globulin (C1), methotrexate (C1), mycophenolate mofetil (C1), cyclosporine A (C1), or tacrolimus (C1) may be considered.

Comments:
If the patient has extensive skin symptoms impairing QOL, systemic therapy may be taken into consideration for the prolonged skin symptoms after the conventional treatment for other organs [6,7] (evidence level VI). No systemic therapy has been proven effective by RCT.
There are case reports describing use of oral dapsone (DDS) [13-15] (evidence level V). In other countries, hydroxychloroquine has also been used [6] (Evidence level VI).
The usefulness of intravenous gamma globulin therapy (IVIg) has been shown by a cross-over study [16] (evidence level II). In this study, significant improvement of the skin symptoms was observed in 8 of 12 DM patients. In addition, there are case reports describing successful use of IVIg [17-19] (evidence level V).
As for immunosuppressants, the usefulness of MTX has been reported by case series studies [20-22] (Evidence level V). Also, the usefulness of mycophenolate mofetil has been reported by case series studies [23,24] (evidence level V). Other case reports have described the usefulness of cyclosporine A and tacrolimus for the treatment of the skin lesions [25-27] (evidence level V). In use of these drugs, careful attention should be paid to possible adverse reactions.
As for biologics, a pilot study has shown the efficacy of rituximab for the treatment of skin symptoms [28] (evidence level III). Another pilot study disclosed limited effectiveness [29] (evidence level III). Regarding TNF inhibitors, a randomized controlled trial of etanercept and prednisone failed to show significant difference despite some skin lesion improvement [30] (evidence level II). Since these biologics have a potent immunosuppressive effect, the decision of application needs careful attention. It should be noted that there are reports describing DM induced by the usage of TNF inhibitors.

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CQ22. How should DM patients with skin calcification be treated?

Recommendation: For calcinosis remaining after standard treatment of DM, administration of low-dose warfarin, diltiazem hydrochloride, aluminum hydroxide, bisphosphonates, probenecid, intravenous gamma globulin, or surgical therapy should be considered. (Recommendation Grade: C1)

Comments:
Calcinosis is a skin symptom that may remain or exacerbate after the improvement of muscle and systemic symptoms. It develops particularly often in juvenile DM patients. In the treatment of the calcinosis, the efficacy of low-dose warfarin [1,2] (evidence level II), diltiazem hydrochloride [3-5] (evidence level V), aluminum hydroxide [6] (evidence level V), bisphosphonate [7-9] (evidence level V), probenecid [10,11] (evidence level V), intravenous gamma globulin [12,13] have been reported although none of them had potent effects. Another option is surgical removal [14] (evidence level V).

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CQ23. Should myositis and malignancy be treated simultaneously in patients with PM/DM and associated-malignancy?

Recommendation: Unless the symptoms of PM/DM require urgent treatment, preceding treatment of the malignancy should be considered.

In patients with PM/DM and associated malignancy, both malignancy (e.g. surgical operations and/or chemotherapy) and myositis (e.g. GC and/or immunosuppressants) should be controlled. However, simultaneous treatments targeting the malignancy and PM/DM may result in delay of wound healing and excessive immunosuppression. In many cases, one of the targets is selected for initial treatment.

Although many case reports on PM/DM associated with malignancy are available, no studies addressed treatment protocol or treatment timing for the two targets. Case series indicated correlation between progression of malignancy and activity of myositis in 8 of 45 cases or 8 of 13 cases [1,2] (evidence level V). Andras C et al. described that levels of creatine kinase and lactate dehydrogenase decreased significantly one month after treatments of the malignancy [3] (evidence level V). Furthermore, several cases went into remission of myositis only by the treatments of malignancy, which did not include GC administration [4-7] (evidence level V). On the other hand, several case reports indicated that treatments of myositis may not be effective without treatments of malignancy, and that response to the treatments of myositis was better after the treatments of malignancy [8,9] (evidence level V). Furthermore, GC administration induces delay of wound healing or excessive immunosuppression, which should be taken into consideration in the surgical operation and chemotherapy. Immunosuppressants may also promote progression of the malignancy.

Based on these notions, treatments of malignancy should be considered first unless treatments of PM/DM are urgent. When the activity of the myositis does not change after the treatments of malignancy, GC with or without immunosuppressants should be initiated. When treatments of the myositis are urgent typically because of severe myositis, dysphagia, respiratory muscle weakness or interstitial lung disease, they should be started after the careful consideration of the risks of the treatments. This can be the case even if the malignancy is not under control.

References

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