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分担研究報告書

多発性筋炎/皮膚筋炎に関する研究

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研究要旨

[研究１:ガイドライン策定]多発性筋炎/皮膚筋炎（PM/DM）は、膠原病内科、皮膚科、神経内科で診療される疾患であるが、我が国における治療方法が必ずしも一定しない。
この問題を解決するために、平成 23 年度研究班から Minds2007 準拠で行われて来た治療ガイドライン策定を完成し、日本リウマチ学会、日本皮膚科学会、日本神経学会とのすりあわせの上、3 学会の承認を得た。さらに、国際的ガイドラインがないことも考慮し、英語版を作成した。
[研究２:国際診断基準検証]一方、国際筋炎分類基準プロジェクト（IMCCP）が提案した分類基準に基づき、我々が収集した PM/DM 群 410 例、Comparator 群 412 例の診断を行い、IMCCP 分類基準の外的妥当性を検討した。その結果、筋生検なし、ありの症例それぞれで感度 88.1%、90.4%、特異度 95.1%、56.9%であり、IMCCP が示した彼らの筋生検なし、ありの症例それぞれ感度 87%、93%、特異度 82%、88%と比べて、筋生検ありの特異度が低く、その他は大概同等であった。これまで利用されてきた、厚生省診断基準の感度 71.0%、特異度　87.1%、古典的国際基準である Bohan and Peter 基準の感度 76.8%、特異度 87.6%と比べれば良好である。従って、本邦でも一定の注意の下、IMCCP 分類基準を採用、利用することが妥当であると考えた。さらに日本の症例に新分類基準をどう適用すべきか、そして疫学調査の結果を他に有効利用できないかを追加検討した。
[研究 3:疫学研究] 2013 年度臨床調査個人票データを用いて、PM/DM の最新の臨床疫学特性を明らかにし、2009 年度との比較を行い疫学特性の経年変化について検討した。2013 年度患者数（有病数）は約 19,000 であり、2003～2013 年度の 11 年間で患者数は 1.5 倍に増加していた。性年齢分布や診断実態（新規登録時の有所見割合）、ステロイドの治療状況、合併症の保有状況などは 2013 年度と 2009 年度の５年間で大きな変化はなかった。一方、新規登録患者でステロイドパルス療法の施行割合や免疫抑制剤の使用割合に増加が認められた。臨床調査個人票は全国規模で経年的に疫学的知見を検討評価できる貴重な資料であり、受給者データの特性を理解したうえで有効活用していくことが望まれる。

A.研究目的

[研究１]多発性筋炎/皮膚筋炎（PM/DM）は、膠原病内科、皮膚科、神経内科で診療される疾患で、診断方法や治療方法が必ずしも一定しない。世界的なこの問題を解決するために、診断のためには我々も加わり国際的診断基準が策定されようとしている。一方、治療に関しては保険診療も問題から国際的ガイドラインではなく地域のガイドラインが対処すべき問題である。
そこで、本研究では、我が国における標準治療の指針とするために策定した治療ガイドラインを日本リウマチ学会、日本神経学会、日本皮膚科学会という３主要学会の認定を得る。さらには、英語版を作成して国際的認知を得る。
[研究 2]PM/D は、筋力低下や皮疹などを主症状とする炎症性筋疾患である。現在、PM/DM の診断基準は国際的には 1975 年に発表された Bohan and Peter の診断基準が、また国内では 1992 年に厚生省自己免疫疾患調査研究班が発表した診断基準が用いられている。いずれも 20 年以上前に作成されたものであり、診断・検査法の進歩に十分対応していないと考えられる。2005 年に国際筋炎分類基準プロジェクト(International Myositis Classification Criteria Project:IMCCP)として作業部会が結成され、国際診断基準策定が開始され、大規模な症例集積が始まり、解析が進められている。2012 年 7 月に IMCCP から封入体筋炎を含む特発性炎症性筋疾患（Idiopathic inflammatory myopathy:IIM）の国際分類基準案（IMCCP 基準案）の初案が公表され、その後修正検討が進められ 2015 年 5 月に分類基準案が確

定・提案されている。なお、IIM には無筋炎型皮膚筋炎（ADM：Amyopathic DM）を含む DM も含まれる。本調査では、わが国の PM/DM 患者の情報を収集し、これを対象として、IMCCP によって示された国際分類基準案（IMCCP 基準案）の妥当性を検討するとともに、IMCCP 案をどのように改善すべきかを検討することを目的とした。

［研究 3］PM/DM は、は、厚生労働省の特定疾患治療研究事業として医療受給対象疾患に指定されてきた。2015 年からは、難病対策の制度変更に伴い、難病法に基づく指定難病として医療費助成対象となっている。これまでの特定疾患治療研究事業は、患者の医療費の自己負担分を公費で補助し、受療を促進することで多くの患者情報を得て病因解明や治療法開発などの調査研究を推進しようとするものである。特定疾患治療研究事業において、臨床調査個人票（個人票）が全ての医療受給申請で提出され、これにより患者（医療受給者）の基本的臨床情報を得ることができる。厚生労働省の難病患者認定適正化事業において、個人票の内容は、都道府県（あるいは保健所）によって、WISH（厚生労働省行政情報総合システム）に導入されている特定疾患調査解析システムに電子入力され、オンラインで厚生労働省へデータが届く仕組みになっている。2003 年度以来、本格的に電子入力されるようになり、その利用が可能となっている。

我々は、1）PM/DM の頻度、性、年齢、発病年齢分布、診断、治療実態、予後等を含めた臨床疫学像を把握・分析すること、2）さらにその分析・活用の疫学的方法の有用性を評価・検討すること、3）その結果に基づき、必要に応じて臨床調査個人票データベースの改善への提言を行うこと、を目的として臨床調査個人票を分析してきた。

これまで、以下（①～③）の分析を行い、疫学的知見を得てきた。①2009 年度臨床調査個人票を用いて、我が国の PM/DM の受給患者数(有病数)の推計、性・年齢・発病年齢分布、診断に関わる臨床所見の有所見割合、治療・治療効果の実態を明らかにした。②2003～2011 年度臨床調査個人票を用いて、罹患率を推計した[3)、5)]。③2011 年度臨床調査個人票を用いて、患者を PM の診断基準を満たす者、DM の診断基準を満たす者に分けて、診断時の有所見割合を明らかにした[6)]。疫学像を継続的に把握、評価していくことは重要である。

本研究の目的は、最新の臨床調査個人票データを用いて、受給患者数（有病数）の推計、性・年齢・発病年齢分布、診断に関わる臨床所見の有所見割合、治療・治療効果などの実態把握を行い、PM/DM の最新の臨床疫学特性を明らかにすること、及び 2009 年度臨床調査個人票の解析で得られた疫学特性（上記①の分析結果）と比較し経年変化について検討することである。

B. 研究方法

［研究 1］平成 23 年度の研究班 PM/DM 分科会メンバー上阪等（分科会長）、冨満弘之（東京医科歯科大学）、太田晶子（埼玉医科大学）、三森経世（京都大学）、川口鎮司（東京女子医科大学）、神田隆（山口大学）、清水潤（東京大学）、藤本学（金沢大学）、室慶直（名古屋大学）、神人正寿（熊本大学）が Minds2007 準拠で治療ガイドライン作成を進めて来た。

これを平成 26 年度から分科会メンバーとなった上阪等（分科会長）、砂田芳秀（川崎医科大学）、太田晶子（埼玉医科大学）、三森経世（京都大学）、川口鎮司（東京女子医科大学）、神田隆（山口大学）、藤本学（金沢大学）、室慶直（名古屋大学）、神人正寿（熊本大学）が引継ぎ、調査と会合を重ね、さらに自己免疫研究班全体での討議も行って、エビデンスに基づく治療ガイドライン策定した。このガイドラインを日本リウマチ学会、日本神経学会、日本皮膚科学会に提出し、会員の意見をフィードバックしてガイドラインに改良を加えた。さらにその英語版を作成した。

［研究 2］1，調査対象

対象は、2007 年 1 月 1 日から 2012 年 12 月 31 日に厚生労働省「自己免疫疾患に関する調査研究班」の研究分担者の施設で確定診断された PM/DM 患者と PM/DM との鑑別を要する非 PM/DM 患者（Comparators）すべてである。ただし、参加各施設の症例数が、PM/DM 患者、非 PM/DM 患者（Comparators）、それぞれ 20 症例を超える場合、確定診断日が新しい患者からもれなくそれぞれ 20 症例を対象とした。また、非 PM/DM 患者（Comparators）については、後述のとおり、一部の疾患に収集症例数の上限を定めた。

患者の選択方法は次のとおりである。

・PM/DM 患者の選定：専門医が PM/DM と確定診断した者（表 1）。

・非 PM/DM 患者（Comparators）の選定：専門医が非 PM/DM と確定診断した者。非 PM/DM には次の疾患を含む(表 1)。疾患名の右に数値を示した疾患については、各施設その数を越えないものとし、診断日が最新の者から選択する。

2，調査方法

対象患者について、既存の臨床データ（診療録）から臨床情報を収集した。これらは、診断・経過に関する既存の臨床データであり、新たな検体収集や測定は行っていない。

2013 年 9 月、調査対象施設に対し調査票を送付し調査を行った。対象となる患者について、別記調査票（表 2）に基づき性、生年月、患者背景、診断年月、診断名、診断に関する所見等の詳細情報を調査した。

提出された症例すべてについて膠原病内科医、神経内科医、皮膚科医の 3 人より構成されるエキスパートグループによって診断を検証した。

収集したデータを用いて、国際分類基準案（IMCCP 基準案）[3)-5)] の他、1992 年厚生省自己免疫疾患調査研

究班の診断基準[2]、Bohan and Peter の分類基準[1]の感度と特異度を算出した。IMCCP 基準案による判定の際、利用する変数の所見が不明、欠損値の場合これを陰性として解析した。また発病年齢が不明の 7 症例については発病年齢が 18 歳未満と同じ扱い（スコア 0 点）として解析した。

3. IMCCP 分類基準案の概要

最近 2015 年 5 月、 IMCCP が提案した分類基準は次のとおりである[5]。診断に使用する検査等の項目それぞれに与えられたスコア（表 3）に基づいて患者それぞれのスコアの合計値（Total score）を求め、スコアの合計値から、その患者が PM/DM である確率 probability(p)を算出する。なお、Skin rash のない患者には筋生検を行うことを必須と提案している。

スコアの合計値（Total score）から probability(p)を求める方法は以下のとおりである。

1) Without Muscle biopsy

Logit(p)=ln(p/(1-p))= -5.33+ Total score

p=exp(-5.33+Total score)/(1+ exp(-5.33+Total score))=1/(1+exp(5.33-score))

2) With Muscle biopsy:

Logit(p)=ln(p/(1-p))= -6.49+ Total score

p=exp(-6.49+Total score)/(1+ exp(-6.49+Total score)) =1/(1+exp(6.49-score))

Probability にカットポイントを設定し、その値を越えた患者を PM/DM と判定する。提案ではカットポイントとして 55%を使った例を示しているが、利用者がその目的に応じてカットポイントを適当に決めるので良いとしている。Total score と Probability の関係は表 4 に示したとおりである。

さらに PM/DM と判定された患者を Subgroup に分ける方法を表 5 のように提案している。Subgroup は PM、IBM、ADM、DM、Juvenile myositis、JDM の 6 つである。

[研究 3]資料として、2016 年の 8 月現在入力済みの、「多発性筋炎・皮膚筋炎」と「強皮症」の臨床調査個人票を利用した。個人票は、厚生労働省に文書で利用申請し、使用許可を得た。

同じ年度に新規、更新両方が入力されていた例については新規のみ採用した。その他、同一個人が重複して入力されていた場合は 1 件のみを採用して解析した。

個人票は必ずしもすべてが電子入力されているのではなく、その割合、入力率を確認することが必要である。そのための分母、受給者の全数を厚生労働統計である衛生行政報告例（7）、（8）から得た。入力率は、電子入力された個人票数／公表された受給者数として求めた。ただし、ここで得られる受給者数全数（入力率の分母）は、多発性筋炎・皮膚筋炎だけのものではなく、多発性筋炎・皮膚筋炎と強皮症の 2 疾患を合せた、「強皮症、皮膚筋炎及び多発性筋炎」の数となっている。多発性筋炎・皮膚筋炎単独での受給者数は 2014 年度までは残念ながらわからない。行政統計上 2 疾患合計の受給者数として公表されているためである。そのため入力率は、「強皮症、皮膚筋炎及び多発性筋炎」の 2 疾患合せた形で算出した。2003～2014 年度の個人票の入力率を確認した。（なお、2015 年の難病法に基づく制度変更以降、衛生行政報告例において 2 疾患別々に受給者数（患者数）が把握されるようになっている）。

有病数の推計方法：多発性筋炎・皮膚筋炎単独の受給者数が公表されていないが、臨床調査個人票では当然、強皮症と多発性筋炎・皮膚筋炎は区別できる。そこで電子入力された個人票の資料を用いて、多発性筋炎・皮膚筋炎単独の受給者数（全数）を推計した。すなわち「皮膚筋炎及び多発性筋炎」の個人票入力件数を、「強皮症」と「皮膚筋炎及び多発性筋炎」の、両者合計「強皮症、皮膚筋炎及び多発性筋炎」の入力率で割ってこれを「皮膚筋炎及び多発性筋炎」の受給者数全数とした。

（倫理面への配慮）

研究 2 では東京医科歯科大学で多施設共同研究として倫理審査を受けるとともに、各参加施設で倫理審査を受け、承認された。

研究 3 では、本研究は、特定疾患治療研究事業における臨床調査個人票の研究目的利用に関する要綱に基づき実施した。利用したデータには、個人名、住所など個人を同定できるものは含まれていない。

C. 研究結果

[研究 1]多発（性）筋炎および皮膚筋炎治療ガイドラインをまとめ、3 学会の承認を得た。また、その英語版を作成した（別添 1）。

[研究 2]

1, 特異自己抗体についての考察

新 IMCCP 分類基準案では、抗体検査としては依然として Jo-1 のみが含まれているが、近年様々な特異自己抗体が同定されている。Jo-1 以外のこれら新しい抗体について、調査票に自由記載できる 9L-25 には、410 例の PM/DM のうち、92 例で表 6 のような抗体の記載が見られた。

興味深いことに、ARS 抗体あるいは EJ 抗体陽性の計 3 例が各施設で PM/DM と診断されているのにも関わらず、新診断基準では非 PM/DM と診断されていた。つまり、新診断基準では診断できない例が存在するが、特異抗体を考慮することでより良い診断基準になる可能性があることが示唆された。

2, 皮疹についての考察

一方、皮疹としては新診断基準ではヘリオトロープ、ゴットロン丘疹、ゴットロン徴候の 3 つが含まれている。今回の疫学調査ではこの 3 つの皮疹の頻度はおおよそ過去の報告通りで(表 7)、ゴットロン徴候がもっとも頻度が高かった。個々の症例で 3 つの皮疹のうちのどれかは存在することが多いと思われ、診察の際に必ず確認すべき皮疹といえるが、410 例中 25 例、つまり 5%以上は診断基準に含まれている 3 つの皮疹が全く

存在しないDMであった。これらの症例は、3つの皮疹以外のmechanic’s handなどの皮疹の存在から判断しているものと思われた。

つまり、比較的な有名なヘリオトロープとゴットロンだけでは診断できない例が存在し、またDMの皮疹というものを理解するうえでは不十分であると考えられた。

3, オッズ比からの考察

続いて、疫学調査で調べた各項目のオッズ比を比較した。

オッズ比の高さは、その項目の診断力の高さを反映している。

オッズ比が高い項目はほとんどが新診断基準に含まれているが(表8)、mechanic’s handや皮膚生検でDMに合致する所見は診断基準案に含まれていない。つまりこれらを考慮することでより精度の高い診断ができる可能性が示唆された。

4, 皮膚科的な見地からの考察

皮膚科的な見地からの解析として、今回の疫学調査では上記の頻度の高いの3つの皮疹(ゴットロン丘疹、ゴットロン徴候、ヘリオトロープ疹)に加えてさらに3つの皮疹を追加で調べた(表7)。

皮膚科を受診するような皮疹がある筋炎と対象疾患のみ抽出して感度と特異度を調べると、もっとも感度特異度とも高く診断に有用なのはゴットロン徴候であった。

逆に疫学調査では134例のPMのうち、爪囲紅斑あるいは爪上皮出血点のような血管病変は10%程度と比較的高頻度に見られた(表9)。多くの専門家はこのような血管病変が存在しても、PMと診断しているということが示された。

最後に、どのような皮疹が抗核抗体やJo-1抗体陽性と相関するのかというのを調べた。まず抗核抗体はV signで一番頻度が高かった(表10)。一般にヘリオトロープ疹、ゴットロン丘疹、ゴットロン徴候、mechanic’s handは物理刺激によって誘発され、爪囲紅斑＋爪上皮出血点は血管障害に、そしてV-signは光線過敏によるものとする考え方があるが、光線過敏が最も免疫異常と関係している可能性がある。

また、Jo-1はmechanic’s handで頻度が高かったが、これはmechanic’s handが抗ARS抗体症候群で頻度が高いという知見と合致するため妥当な結果と考えられた。

[研究3]）個人票入力率（2016年8月現在）

「皮膚筋炎及び多発性筋炎」と「強皮症」の２疾患合せた個人票入力件数、入力率を表1に示した。2003年度から2014年度の各年の「強皮症、皮膚筋炎及び多発性筋炎」の全受給者数は約32,000～53,000であり、2003年度から2014年度の個人票電子入力件数（2013年7月現在）は、約19,000～35,000であった。2003年度から2013年度の各年入力率は48.8%～81.5%であった。2014年度は10%と低かった。都道府県別に入力率をみると、その格差は大きく、ほぼ100%の入力をしているところもあれば全く入力していない県もあった。また同じ都道府県でも入力状況は年次によって異なっていた。なお、2014年度の入力率は10%と低いため、疫学像把握の解析においては対象外とした。

「強皮症」と「皮膚筋炎及び多発性筋炎」の入力件数の内訳は表２のとおりである。

２）多発性筋炎・皮膚筋炎の受給者数の推計

「皮膚筋炎及び多発性筋炎」の臨床調査個人票入力件数と推計受給者数を表３に示した。各年の「皮膚筋炎及び多発性筋炎」の入力件数を、各年の（「強皮症、皮膚筋炎及び多発性筋炎」の）入力率で割り戻し、「皮膚筋炎及び多発性筋炎」の全受給者数を推計している。2013年度の「皮膚筋炎及び多発性筋炎」の全受給者数は約19,000人、新規受給者数は約2,000人と推計された。2003～2013年度の11年間で全受給者数は1.5倍に増加していた。

３）多発性筋炎・皮膚筋炎の臨床疫学特性

臨床疫学特性をみるために、入力率がある程度高くかつ最新年である2013年度データ（入力率48.8%）を解析対象とした。経年比較のため2011年度の班研究における2009年度データ(入力率80%）解析結果をあわせて示した[1)、2)]。

「皮膚筋炎及び多発性筋炎」の2013年度の性別入力患者数を表４に示した。入力患者数は9,499(男2,602、女6,897)、性比（女/男）は2.65であった。

2013年度、2009年度受給者（患者）の年齢分布を図１、図２にそれぞれ示した。2013年度、2009年度ともに、男女とも60歳代にピークを認めた。男のピークは65-69歳、 女は60-64歳と女の最頻値のほうがやや若年であり、この傾向も両年度で変わらなかった。

2013年度、2009年度受給者の発病年齢分布を図３、図４にそれぞれ示した。発病年齢のピークは男女とも50歳代であり、発病年齢は現在年齢よりも10歳程若い。これらの特徴は両年度で変わらなかった。

新規登録時の臨床症状・所見の有所見割合について、2013年度、2009年度の所見を表５、表６にそれぞれ示した。更新者の臨床症状・所見についても同様に、表７、表８に示した。2013年度において、新規登録患者では筋力低下、筋痛・筋把握痛、血清筋原性酵素の上昇を高率（70－90%）に認めた。しかし一方では、侵襲的な針筋電図や筋生検を施行した例は半数に満たず、筋の生理的、病理的状態の把握はなされずに診断されていた。抗Jo-1抗体陽性は13%であった。これらの傾向は2009年度と大きく変わらなかった（表５、表６）。

新規登録時の治療状況を、2013年度、2009年度について、表９、表10にそれぞれ示した。更新者についても同様に表11、表12に示した。ステロイド治療は90%以上で行われ、95%以上の症例で効果を認めた（表９、表 11）。新規患者の免疫抑制剤の使用は 2009 年度24.9%から2013年度32.1%へと増加していた（表９、表10)。更新者においても全経過を通じた使用状況は、2009年度40.3%から2013年度52.1%に増加していた

（表 11、表 12)、新規患者のステロイドパルス療法も、2009 年度 24.7%から 2013 年度 32.9%へと増加していた（表９、表 10)。

合併症については、新規患者の約半数で間質性肺炎を、また約 10%に悪性腫瘍を合併しており、これらも 2013 年度、2009 年度で頻度に大きな違いはなかった(表５、表 13、表 14)。悪性腫瘍の合併は、全経過で増加はせず、ステロイド治療による副作用と考えられる合併症が増えていた(表 15)。これらの傾向も 2013 年度、2009 年度でほぼ変わりはなかった(表 15、表 16)。ほとんどの症例で、治療効果を認めていたが、半数以上の患者で筋力低下が残存し、約 4 割の患者は間質性肺炎を合併している状況も、2013 年度、2009 年度で変わりはなかった（表７、表８)。

D. 考察

[研究１]本ガイドラインは学会で承認を受けたものとなった。今後、国際社会に向けて発信する予定である。
[研究 2] 新診断基準案では少なくとも、特異自己抗体と皮疹で不十分な点がある可能性がある。最近 ARS 抗体、さらには Mi2 抗体、MDA5 抗体そして TIF1 抗体が本邦では相次いで保険収載されていることもあり、それら特異抗体と mechanic’s hand、皮膚生検を診察の際に追加で考慮すればより良い診断ができる可能性がある。

また、PM と DM は皮疹の有無で分けるという考えが一般的であるが、血管病変については PM でも見られるとエキスパートが考えていることがうかがわれた。
[研究 3]　今回の 2013 年度データの解析で、現在、多発性筋炎・皮膚筋炎の患者数（受給者数）は約 19,000 人であり、年間約 2,000 人が新規受給登録していることがわかった。また 2003～2013 年度の 11 年間で患者数は 1.5 倍に増加していた。
患者性比（女/男）は 2.65 と女で多く、中年以降の発症が多い。男女とも 60 歳代にピークを認めた。発病年齢のピークは男女とも 50 歳代であり、発病年齢は現在年齢よりも 10 歳程若い。これらの特徴は 2009 年度のものと違いはなかった。ただし、受給者データの特性から年齢分布に関しては、小児の患者数は過小評価の可能性がある。小児医療費は各自治体からの医療費助成があるため、受給登録をしないことが多いと考えられるためである。

2013 年度の、新規登録時（診断時）の臨床症状・所見は 2009 年度のそれと大きな変わりはなく、診断手段・実態に大きな変化はないと考えられた。

2013 年度の治療状況は、90%以上でステロイドが使用されており、これは 2009 年度と変わりはなかった。一方、新規登録患者でステロイドパルス療法の施行割合や免疫抑制剤の使用割合に増加が認められた。新規発症例で早期から免疫抑制剤が併用されていることが伺えた。
治療効果については、95%の症例でステロイドの有効性は認められているが、治療にも関わらず過半数の症例で筋力低下を残しているといった状況であり、これらは 2009 年度と変わりはなかった。
臨床調査個人票を利用して、最新の多発性筋炎・皮膚筋炎の臨床疫学特性が明らかになった。ただし、個人票データにはいくつかの問題点もある。個人票の記載内容の正確性、診断の妥当性や、先に小児の例で示したような患者が受給するかどうかの社会経済的要因の影響をうけること、などである。これらのデータ特性を考慮した上で結果を解釈し、有効活用していくことが望まれる。
個人票は全国規模で経年的に疫学的知見を検討評価できる貴重な資料であり、また得られた知見は個人票の改訂の検討資料に資すると考えられ、継続的な活用が望まれる。

E. 結論

我が国発の PM/DM に関する治療ガイドライン案が策定され、国際診断基準の妥当性が検証された。

疫学研究では、最新の多発性筋炎・皮膚筋炎の疫学特性を明らかにした。2013 年度患者数（有病数）は約 19,000 であり、2003～2013 年度の 11 年間で患者数は 1.5 倍に増加していた。新規登録患者でステロイドパルス療法の施行割合や免疫抑制剤の使用割合に増加が認められた。

F. 健康危険情報

特になし。

G. 研究発表

1. 論文発表

なし

2. 学会発表

Jinnin M. International Classification Criteria The 13th International Workshop on Autoantibodies and Autoimmunity,10/11-13/2016 Kyoto

H. 知的財産権の出願・登録状況（予定を含む）

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

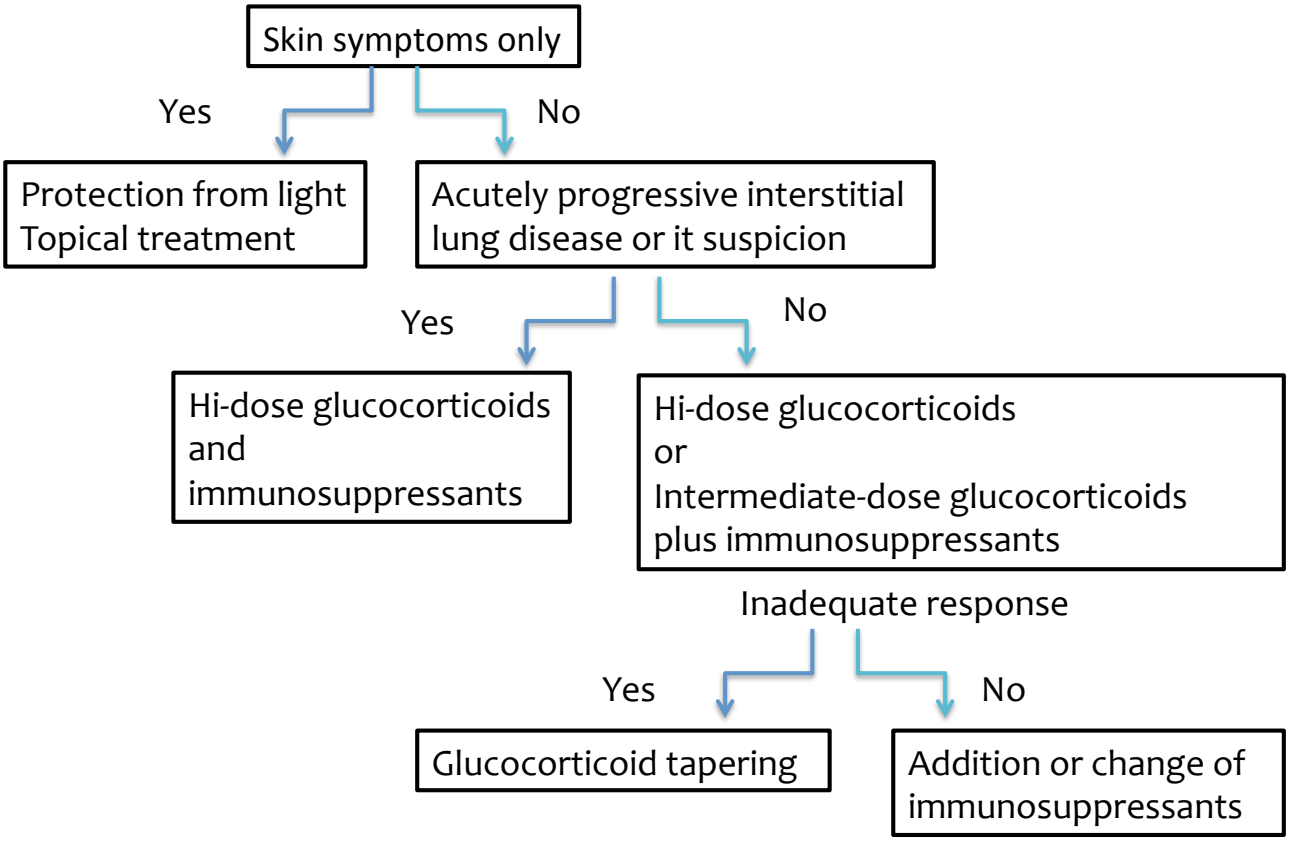
なし

別添１　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.

Hitoshi Kohsaka, Tsuneyo Mimori, Takashi Kanda, Jun Shimizu, Yoshihide Sunada, Manabu Fujimoto, Yasushi Kawaguchi, Masatoshi Jinnin, Yoshinao Muro, Shoichiro Ishihara, Takayuki Sumida

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.

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表 1 疾患別患者数

疾患別患者数:PMDM

	総数		sex				kamei					
			男		女		1膠原病内科		2神経内科		3皮膚科	
	n	%	n	%	n	%	n	%	n	%	n	%
総数	410	100	118	100	292	100	263	100	57	100	90	100
d_name												
1 Polymyositis(PM)	134	32.7	39	33.1	95	32.5	101	38.4	25	43.9	8	8.9
2 Dermatomyositis(DM)	188	45.9	61	51.7	127	43.5	108	41.1	26	45.6	54	60
3 Amyopathic dermatomyositis(ADM)	64	15.6	13	11	51	17.5	41	15.6	5	8.8	18	20
4 Hypomyopahic dermatomyositis	18	4.4	2	1.7	16	5.5	9	3.4	1	1.8	8	8.9
5 Juvenile dermatomyositis	6	1.5	3	2.5	3	1	4	1.5	.	0	2	2.2

疾患別患者数:Comparators

	総数		sex				kamei					
			男		女		1膠原病内科		2神経内科		3皮膚科	
	n	%	n	%	n	%	n	%	n	%	n	%
総数	412	100	115	100	297	100	267	100	72	100	73	100
d_name												
9 Fascioscapulohumeral dystrophy	2	0.5	1	0.9	1	0.3	.	0	2	2.8	.	0
10 Limb-girdle dystrophy	5	1.2	2	1.7	3	1	.	0	5	6.9	.	0
11 Myotonic dystrophy	3	0.7	2	1.7	1	0.3	.	0	3	4.2	.	0
12 Other dystrophy	12	2.9	6	5.2	6	2	.	0	12	16.7	.	0
13 Dysferlinopathy	1	0.2	1	0.9	.	0	.	0	1	1.4	.	0
14 Bacterial myopathy	1	0.2	1	0.9	.	0	1	0.4	.	0	.	0
16 Drug or toxin associated myopathy	1	0.2	1	0.9	.	0	.	0	1	1.4	.	0
19 Hypereosinophilic syndrome	5	1.2	2	1.7	3	1	4	1.5	.	0	1	1.4
21 Hypokalemia	2	0.5	2	1.7	.	0	.	0	2	2.8	.	0
22 Immune-mediated necrotizing	3	0.7	3	2.6	.	0	.	0	3	4.2	.	0
23 Inclusion body myositis	7	1.7	6	5.2	1	0.3	1	0.4	6	8.3	.	0
24 Rimmed vacuolar distal	4	1	3	2.6	1	0.3	1	0.4	3	4.2	.	0
25 Juvenile idiopathic arthritis	1	0.2	.	0	1	0.3	1	0.4	.	0	.	0
27 Mitochondrial myopathy	8	1.9	5	4.3	3	1	.	0	8	11.1	.	0
28 Mixed connective tissue disease	49	11.9	4	3.5	45	15.2	43	16.1	4	5.6	2	2.7
29 Systemic lupus	88	21.4	11	9.6	77	25.9	79	29.6	2	2.8	7	9.6
30 Systemic sclerosis	60	14.6	10	8.7	50	16.8	45	16.9	2	2.8	13	17.8
31 Systemic vasculitis	63	15.3	25	21.7	38	12.8	50	18.7	12	16.7	1	1.4
32 Viral myopathy	1	0.2	1	0.9	.	0	.	0	1	1.4	.	0
33 Seborrheic dermatitis	4	1	1	0.9	3	1	.	0	.	0	4	5.5
34 Contact dermatitis	9	2.2	2	1.7	7	2.4	1	0.4	.	0	8	11
35 Hand eczema	7	1.7	2	1.7	5	1.7	.	0	.	0	7	9.6
36 Sweet s disease	2	0.5	1	0.9	1	0.3	1	0.4	.	0	1	1.4
37 Thyroid dysfunction	3	0.7	2	1.7	1	0.3	2	0.7	1	1.4	.	0
38 Photosensitive dermatitis	6	1.5	3	2.6	3	1	.	0	.	0	6	8.2
39 Erysipelas	4	1	2	1.7	2	0.7	.	0	.	0	4	5.5
40 Drug eruption	4	1	1	0.9	3	1	.	0	.	0	4	5.5
41 Erythematosus other than SLE	2	0.5	1	0.9	1	0.3	.	0	.	0	2	2.7
42 Angioedema	2	0.5	.	0	2	0.7	.	0	.	0	2	2.7
43 Adult Still s disease	32	7.8	7	6.1	25	8.4	32	12	.	0	.	0
44 Sarcoidosis	14	3.4	4	3.5	10	3.4	4	1.5	4	5.6	6	8.2
45 Verruca vulgaris	2	0.5	.	0	2	0.7	.	0	.	0	2	2.7
47 Lymphoma	5	1.2	3	2.6	2	0.7	2	0.7	.	0	3	4.1

表2　**多発(性)筋炎/皮膚筋炎(PM/DM)の国際診断基準の妥当性に関する疫学調査」調査票**

（別紙記載要領をご参照下さい）

記載年月日　西暦　2013年　　月　　日

記載者	所属施設名	
	氏名	
	担当科名	1. 膠原病内科　2. 神経内科　3. 皮膚科　4.その他（　　）

患者	一連番号		
	性別	1. 男　2. 女	
	生年月	西暦　　年　　月	
	発病年月	西暦　　年　　月　発病時年齢　　歳	
	初診年月	西暦　　年　　月	
	確定診断年月	西暦　　年　　月	
	診断名	1. PM/DM 2. 非 PM/DM	（記載要領にある表1の疾患名を疾患番号とともに記載）

診断時所見（診断に用いた、診断確定までに現れた所見を、必ずしも診断時点になくても、記載）

筋所見			
1M. 進行性の上肢近位筋筋力低下（対称性）	1.あり	2.なし	3.不明
5M. 手関節・手指屈筋の筋力低下が同側肩関節外転筋より強い	1.あり	2.なし	3.不明
8M. 進行性の下肢近位筋筋力低下（対称性）	1.あり	2.なし	3.不明
16M. 頸部の屈筋群優位の筋力低下	1.あり	2.なし	3.不明
17M. 近位優位の下肢筋力低下	1.あり	2.なし	3.不明
18M. 近位優位の上肢筋力低下	1.あり	2.なし	3.不明
21M. 筋の把握痛	1.あり	2.なし	3.不明

皮膚所見			
1S. ヘリオトロープ疹	1.あり	2.なし	3.不明
2S. ゴットロン丘疹	1.あり	2.なし	3.不明
3S. ゴットロン徴候	1.あり	2.なし	3.不明
5S. V-neck徴候	1.あり	2.なし	3.不明
7S. Linear extensor erythema	1.あり	2.なし	3.不明
9S. 爪囲紅斑あるいは爪郭部毛細血管異常	1.あり	2.なし	3.不明
10S. Mechanic's hands	1.あり	2.なし	3.不明

他の臨床所見			
1O. 自己免疫性疾患の家族歴（記載要領の表2参照）	1.あり	2.なし	3.不明
2O. 筋疾患の家族歴（記載要領の表3参照）	1.あり	2.なし	3.不明
3Oa. 発症形式が急性（2週間以内）	1.あり	2.なし	3.不明
5O. 関節炎	1.あり	2.なし	3.不明
→関節炎ありの場合の骨破壊	1.伴う	2.伴わない	3.不明
6O. 多関節痛	1.あり	2.なし	3.不明
→多関節痛ありの場合の骨破壊	1.伴う	2.伴わない	3.不明
8O. 原因不明の発熱	1.あり	2.なし	3.不明
9O. 間質性肺炎	1.あり	2.なし	3.不明
10O. 嚥下障害、食道蠕動障害	1.あり	2.なし	3.不明
13O. ステロイド・免疫抑制剤投与による症状の改善	1.あり	2.なし	3.不明

筋生検所見

0B. 筋生検施行	1.あり	2.なし	
（筋生検施行ありの場合以下1B～12Bを記載）			
1B. タイプI、II線維の壊死、貪食、筋線維の変性	1.あり	2.なし	3.不明
3B. 筋線維束内への単核球浸潤（筋線維には浸潤しない）	1.あり	2.なし	3.不明
4B. 単核球浸潤が見られる非壊死線維	1.あり	2.なし	3.不明
5B. 筋線維束周囲と/または血管周囲への単核球浸潤	1.あり	2.なし	3.不明
6B. Perifascicular atrophy	1.あり	2.なし	3.不明
8B. Rimmed vacuoles	1.あり	2.なし	3.不明
11B. 免疫組織化学の利用	1.あり	2.なし	
（免疫組織化学の利用ありの場合以下12Bを記載）			
12B. MHC class I 発現の亢進した線維	1.あり	2.なし	3.不明

臨床検査所見（経過中最も著明な異常値）	検査値	単位	正常上限値
1L. 血清CK値			
2L. 血清LDH値			
3L. 血清AST（ASAT/SGOT）値			
4L. 血清ALT(ALAT/SGPT)値			
5L. 血清アルドラーゼ値			
6L. 赤沈（1時間値）			
7L. CRP値			

8L. 自己抗体検査	1.あり	2.なし	
（自己抗体検査ありの場合以下9L-1～9L-25を記載）			
9L-1. 抗核抗体	1.陽性	2.陰性	3.未検
9L-2. 抗Jo-1 抗体	1.陽性	2.陰性	3.未検
9L-9. 抗SSA/Ro抗体	1.陽性	2.陰性	3.未検
9L-12. 抗SSB/La抗体	1.陽性	2.陰性	3.未検
9L-13. 抗RNP(U1RNP)抗体	1.陽性	2.陰性	3.未検
9L-16. 抗Centromere B抗体(ACA)	1.陽性	2.陰性	3.未検
9L-17. 抗Topoisomerase-1/Scl70抗体	1.陽性	2.陰性	3.未検
9L-19. 抗Sm抗体	1.陽性	2.陰性	3.未検
9L-24. 抗CCP抗体	1.陽性	2.陰性	3.未検
9L-25. 他の自己抗体（　　）	1.陽性	2.陰性	3.未検
筋電図所見			
筋電図施行	1.あり	2.なし	
（筋電図施行ありの場合以下1、2を記載）			
1. 線維自発電位、陽性鋭波、complex repetitive dischargeなどの所見	1.あり	2.なし	3.不明
2. 短持続・低電位な多相性運動単位活動電位(MUAPs)	1.あり	2.なし	3.不明
MRI所見			
MRI施行	1.あり	2.なし	
（MRI施行ありの場合以下1、2を記載）			
1. STIRまたはT2WIでの筋浮腫	1.あり	2.なし	3.不明
2. T1WIでの筋萎縮、筋の脂肪化など	1.あり	2.なし	3.不明
皮膚生検			
皮膚生検施行	1.あり	2.なし	
（皮膚生検施行ありの場合以下13Lを記載）			
13L. 皮膚筋炎に合致する所見	1.あり	2.なし	3.不明

表3

The EULAR/ACR classification criteria for idiopathic inflammatory myopathies

Variable	Score	
	Without muscle biopsy data	With muscle biopsy data
18 ≤ Age of onset of first symptom assumed to be related to the disease < 40	1.3	1.5
Age of onset of first symptom assumed to be related to the disease ≥ 40	2.1	2.2
Muscle weakness		
Objective symmetric weakness, usually progressive, of the proximal upper extremities	0.7	0.7
Objective symmetric weakness, usually progressive, of the proximal lower extremities	0.8	0.5
Neck flexors are relatively weaker than neck extensors	1.9	1.6
In the legs proximal muscles are relatively weaker than distal muscles	0.9	1.2
Skin manifestations		
Heliotrope rash	3.1	3.2
Gottron´s papules	2.1	2.7
Gottron's sign	3.3	3.7
Other clinical manifestations		
Dysphagia or esophageal dysmotility	0.7	0.6
Laboratory measurements		
Anti-Jo-1 (anti-Histidyl-tRNA synthetase) autoantibody positivity	3.9	3.8
Serum creatine kinase activity (CK) activity *or* Serum lactate dehydrogenase (LDH) activity *or* Serum aspartate aminotransferase (ASAT/AST/SGOT) activity *or* Serum alanine aminotransferase (ALAT/ALT/SGPT) activity	1.3	1.4
Muscle biopsy features		
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		1.7
Perimysial and/or perivascular infiltration of mononuclear cells		1.2
Perifascicular atrophy		1.9
Rimmed vacuoles		3.1

表4　Total score とprobabilityの関係

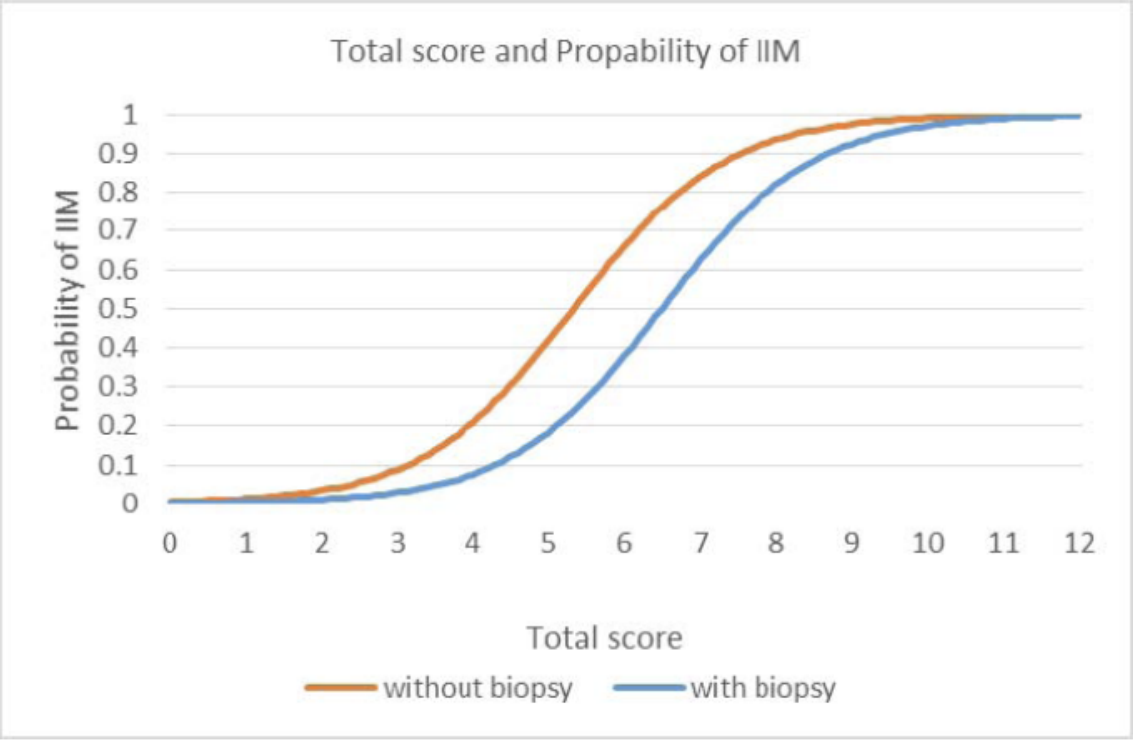

表5

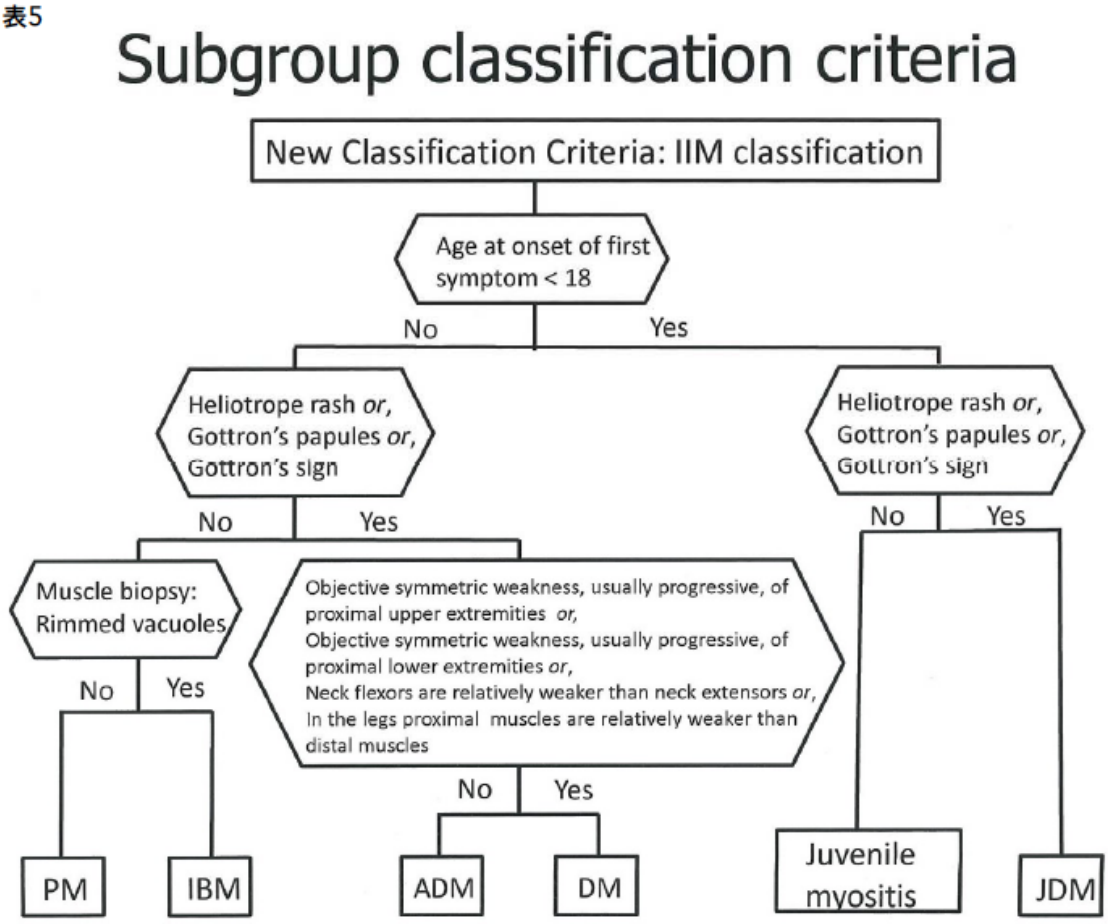

表6

ARS	3	2例は新診断基準で非PM/DMと診断された
PL-7	5	
PL-12	3	
EJ	3	1例は新診断基準で非PM/DMと診断された
OJ	1	
Mi-2	15	
TIF1Γ	12	
MDA5	34	
NXP2	1	
p155	3	
PM-Scl	1	
Ku	2	
SRP	9	
total	**92 PM/DM**	

表7

	感度	特異度
ヘリオトロープ疹	45.3%	83.1%
ゴットロン丘疹	65.3%	85.4%
ゴットロン徴候	81.0%	87.6%
mechanic's hand	38.4%	89.9%
爪囲紅斑＋NFB	62.4%	42.7%
V-sign	37.4%	79.8%

表8

オッズ比= PM/DMにおける陽性者数/陰性者数
非PM/DMにおける陽性者数/陰性者数

17M. 近位優位の下肢筋力低下	12.05
18M. 近位優位の上肢筋力低下	13.22
1S. ヘリオトロープ疹	11.57
2S. ゴットロン丘疹	24.36
3S. ゴットロン徴候	45.07
10S. Mechanic's hands	15.97
6B. Perifascicular atrophy	22.42
9L-2. 抗Jo-1抗体陽性	24.69
13L. 皮膚筋炎に合致する所見	49.92

表9

	n=
ヘリオトロープ疹	0
ゴットロン丘疹	2
ゴットロン徴候	3
mechanic's hand	4
爪囲紅斑＋NFB	13
V-sign	1

表10

		抗核抗体	Jo-1
物理刺激	ヘリオトロープ疹	58.8%	9.4%
	ゴットロン丘疹	56.5%	7.7%
	ゴットロン徴候	55.7%	10.2%
	mechanic's hand	47.8%	15.6%
血管障害	爪囲紅斑＋NFB	57.0%	5.6%
光線過敏	V-sign	70.0%	4.2%