Developing standardised treatment for adults with myositis and different phenotypes: an international survey of current prescribing preferences

S. Tansley[1,2], G. Shaddick[2], L. Christopher-Stine[3], C. Sharp[4], L. Dourmishev[5], B. Maurer[6], H. Chinoy[4,7], N. McHugh[1,2]

[1]Royal National Hospital for Rheumatic Diseases, Royal United Hospitals Foundation Trust, Bath, UK; [2]University of Bath, UK; [3]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [4]Salford Royal NHS Foundation Trust, UK; [5]Department of Dermatology and Venereology, Medical University of Sofia, Bulgaria; [6]Department of Rheumatology, University Hospital Zurich, Switzerland; [7]National Institute of Health Research Manchester Musculoskeletal Biomedical Research Unit, Centre for Musculoskeletal Research, University of Manchester, UK.

Abstract

Objective

The evidence base for treatment of the idiopathic inflammatory myopathies is extremely limited. The rarity and heterogeneity of these diseases has hampered the development of good quality clinical trials and while a range of immunomodulatory treatments are commonly used in clinical practice, as yet there are no clear guidelines directing their use. We aimed to establish current prescribing regimens used to treat adults with myositis internationally.

Methods

An electronic survey based on different clinical scenarios was distributed internationally to clinicians involved in the treatment of patients with myositis. Participants were asked to select their first-line treatment preferences in each situation. A multinomial regression analysis was used to assess the influence of clinical scenario, respondent expertise and country of origin on first-line treatment choice.

Results

107 survey responses were received. 57% of respondents considered themselves an expert in myositis and the majority of respondents were rheumatologists although responses from other specialities were also received. Pharmacological treatment with steroids and additional immunotherapy was the preference in most scenarios. First-line immunosuppressant choice was significantly influenced by the clinical scenario, the expertise of the treating physician and country of practice. Azathioprine, methotrexate and mycophenolate mofetil were the most commonly chosen agents.

Conclusion

In the absence of available evidence, clinical experience and expert consensus often forms the basis of treatment guidelines. These results suggest that an international consensus approach would be possible in myositis and would overcome an urgent, yet unmet need for patients suffering with this difficult disease.

Key words

myositis, treatment, immunosuppressant, muscle disease

Sarah Tansley, MBChB
Gavin Shaddick, PhD
Lisa Christopher-Stine, MD, MPH
Charlotte Sharp, MBChB, MRCP
Lyubomir Dourmishev, MD, PhD
Britta Maurer, MD
Hector Chinoy, PhD, FRCP
Neil McHugh, MBChB, MD

Please address correspondence to:
Sarah Tansley,
Royal National Hospital for Rheumatic Diseases,
Royal United Hospitals NHS Foundation Trust,
Bath BA1 1RL, UK.
E-mail: s.tansley@nhs.net

Received on November 24, 2015; accepted in revised form on February 15, 2016.

Funding: S. Tansley is supported by a fellowship funded by the Bath Institute for Rheumatic Diseases.
L. Christopher-Stine is supported by the Huayi and Suiling Zhang Discovery Fund.
This work has also been support by an Arthritis Research UK grant (18474) and Myositis UK.
This publication was supported by researchers at the National Institute for Health Research (NIHR) Biomedical Research Unit Funding Scheme.
The views expressed are those of the authors and not necessarily those of the (UK) National Health Service (NHS), the NIHR or the (UK) Department of Health.

Competing interests: L. Christopher-Stine reports personal fees from Novartis, personal fees from Mallinckdrodt, personal fees from Walgreens, from Idera Pharmaceuticals, from Marathon Pharmaceticals, from Ono Pharma UK Ltd, from null, outside the submitted work; L. Christopher-Stine also has a patent for Detection of HMGCoA reductase (HMGCR) Antibodies in Patient Sera, JHU C-11077 with royalties paid.
The other co-authors have declared no competing interests.

Introduction

The idiopathic inflammatory myopathies (IIM) are a collection of rare diseases characterised by muscle weakness. Associated features include malignancy, interstitial lung disease and skin disease. Even within the traditional subtypes of polymyositis, dermatomyositis and inclusion body myositis there is considerable heterogeneity including, paradoxically, some forms with limited or no muscle involvement. Sub-classification of patients by autoantibody status has been shown to facilitate patient subdivision into more homogenous groups but, while autoantibodies are now detectable in the majority of adults with IIM, as yet comprehensive autoantibody screening is only available in a limited number of centres (1). The rarity of IIM combined with disease heterogeneity has hampered the development of good quality clinical trials and as reported in a Cochrane and other systematic literature reviews the evidence base for treatment remains very limited (2-4). Appropriate patient stratification in future trials is likely to be crucial, particularly as there is emerging evidence that selected patients may benefit more from certain treatments than others (5). While immunosuppression in various guises remains the mainstay of treatment for IIM there is no evidence, consensus or accepted guideline to indicate agent preference. This choice is therefore made based on the experiences and personal preferences of the prescribing physician.

As part of the STAMP (**S**tandardised **T**reatment for **A**dults with **M**yositis and different **P**henotypes) project developed within the International Myositis Assessment and Clinical Studies Group (IMACS), we sought to establish the prescribing preferences for clinicians treating adult patients with different sub-types of IIM, with the aim of establishing whether an international consensus guideline would be feasible.

Methods

In consultation with IMACS we created a survey based on eight clinical scenarios designed to reflect different IIM subtypes. Fictional case vignettes were based on serological subtypes of IIM but autoantibody status was not included unless laboratory testing was readily available. We questioned what immunosuppressive treatment survey respondents felt to be appropriate, if any. In order to minimise bias, immunosuppressant options were the same in each scenario and presented in alphabetical order. See supplementary information for case scenarios used.

The web-based survey was available between 26th March and 31st July 2013 and the link was distributed via the British Society for Rheumatology electronic newsletter and emailed to national and international special interest groups (UkMyoNet, EUMyoNet and IMACS). Recipients were asked to forward the survey on to colleagues via their own networks, in order to reach as wide an audience as possible.

Surveys were completed anonymously. However, we asked that respondents were at consultant/attending physician level and additional demographic data was collected including location and type of practice, number of years in practice, number of IIM patients seen, IMACS membership and whether the respondent considered themselves an expert, or had a special interest, in myositis.

Statistical analysis

All analyses were performed using the R statistical package (6). Initial data analysis consisted of investigating the large number of treatment choices and the inter-relationship between first-line treatments, the latter of which were displayed graphically as a chord diagram. Multinomial regression was used to assess the influence of variables such as expert status, clinical scenario, country of origin on the choice of treatment. Specialty specific treatment preferences were not explored due to low numbers of non-rheumatologist responses.

Results

Respondents

107 survey responses were received, the majority (90) from consultant rheumatologists, but also from neurologists (8), dermatologists (4) and general physicians/internists (5). Just under half of

the responses came from UK-based physicians. Scenarios were presented in numerical order and the number of responses reduced through the series of cases. Sixty-seven respondents completed Scenario 8. Overall 57% of respondents considered themselves an expert, or had a special interest, in myositis. Non-expert respondents were primarily based in the UK or Australia (Table I). There was an even spread of length of time in practice amongst respondents. Predictably, self-reported experts saw a higher median number of IIM patients per year than non-experts (30 (IQR 15-61) *vs*. 5 (IQR3-8)).

First-line treatment

Pharmacological treatment with steroids and additional immunotherapy was the preference in most scenarios (Table II). For those who felt pharmacotherapy beyond corticosteroids was appropriate immunosuppressant preferences are shown in Supplementary Figure 1. First-line immunosuppressant preferences were defined as one of the respondents' top three choices. More than one 'first choice' treatment could therefore be selected. The relationship between treatment choices across all scenarios was examined and is represented graphically in Supplementary Figure 2. Respondents often selected the same drug(s) in multiple scenarios and the most popular choices were often selected together by respondents as their first-line choice(s).

Clinical scenario influences treatment choice

The prescription of all immunosuppressant medications was influenced by the clinical scenario ($p<0.0001$), with for example, the probability of azathioprine being prescribed first-line significantly lower in scenarios 5 ($p=0.003$), 6 ($p=0.007$), 7 ($p=0.024$) and 8 ($p<0.001$) than scenario 1. Similarly, the probability of mycophenolate mofetil being prescribed as a first line drug was significantly lower in scenarios 5 ($p=0.001$), 7 ($p=0.001$), and 8 ($p<0.001$) compared to scenario 1, and methotrexate significantly higher in scenarios 2 ($p=0.011$), 3 ($p<0.001$), 4 ($p<0.001$), 6 ($p=0.048$) and 7 ($p=0.034$).

Table I. Demographics of survey responders. The majority of survey respondents specialised in rheumatology. Non-expert responses predominantly came from the UK and Australia.

Country of practice	Specialty	Experts (%)	IIM patients seen/year Median (IQR)
Argentina	5 R	4 (80)	13 (7.5-13.5)
Australia	11 R, 2 N	2 (15)	5 (3-8)
Bulgaria	3 D	3 (100)	15 (15-16)
Canada	3 R	3 (100)	20 (16-25)
China	2 R	2 (100)	150 (125-175)
Columbia	1 R	1 (100)	9
Czech Republic	2 R	2 (100)	77 (69-85)
Hungary	2 GM	2 (100)	251.5 (162.75-340.75)
India	1 R	1 (100)	16
Japan	3 R	3 (100)	40 (27.5-42.5)
Mexico	1 R	1 (100)	52
Netherlands	1 GM, 1 N	2 (100)	25.5 (17.25-33.75)
Poland	2 R	1 (50)	31.5 (24.75-38.25)
South Korea	1 R	1 (100)	60
Spain	1 R, 2 GM	3 (100)	20 (15-47.5)
Switzerland	1 R	1 (100)	200
United Kingdom	47 R, 4 N, 1 D	19 (37)	8 (4-17)
United States	9 R, 1 N	10 (100)	57.5 (42-121.25)
Total	**90 R, 8 N, 4 D, 5 GM**	**61 (57)**	**13 (5-41.5)**

R: rheumatology; N: neurology; D: dermatology; GM: general/internal medicine.

Table II. Treatment recommendations for each scenario. Pharmacological treatment with steroids and additional immunotherapy was the preference in most scenarios. For details of the case vignettes used see supplementary material.

	Pharmacological treatment recommended (%)	Preferred route of steroid administration (%)			Additional immunotherapy recommended beyond steroids (%)
		IV	Oral	Topical	
Scenario 1: ASS & anti-Jo-1	98	25	75	0	95
Scenario 2: Cancer associated DM	100	34	66	0	82
Scenario 3: DM	97	20	80	0	83
Scenario 4: NAM & anti-SRP	97	64	36	0	94
Scenario 5: IBM	75	19	81	0	52
Scenario 6: CADM & anti-MDA5 cutaneous features	93	24	69	7	89
Scenario 7: NAM & statin history	98	12	88	0	65
Scenario 8: CADM	95	1	63	36	68

ASS: anti-synthetase syndrome; DM: dermatomyositis; NAM: necrotising autoimmune myositis; IBM: inclusion body myositis; CADM: clinically amyopathic myositis.

Certain scenarios appeared to provoke a more 'aggressive' treatment approach; this was particularly apparent in scenario 4 (necrotising autoimmune myopathy and anti-SRP autoantibodies) where 64% of respondents felt intravenous (IV) corticosteroids were preferable. Interestingly, this was also the scenario that saw the highest use of IV immunoglobulin as a first-line option, although this was non-significant and other agents (azathioprine and methotrexate) were more commonly selected. Scenario 1 (anti-synthetase syndrome and anti-Jo-1 autoantibodies) also generated an aggressive approach with IV cyclophosphamide the most popular treatment choice and both IV immunoglobulin and IV cyclophosphamide being significantly more likely to be prescribed in this scenario than the others ($p<0.0001$). In contrast, in the absence of muscle or organ involvement (scenario 8: Clinically amyopathic dermatomyositis) the management approach was much less aggressive: Whilst 95% respondents agreed treatment was indicated, 31% of those did not recommend immunosuppression beyond prednisolone and in 36% topical prednisolone was felt

to be the most appropriate with only 1 respondent preferring the IV route. Additional agents, where recommended, were often less potent with both hydroxychloroquine ($p<0.001$) and topical tacrolimus popular choices ($p=0.001$).

Experts versus non-expert status

Overall azathioprine, methotrexate and mycophenolate mofetil were the most popular treatment choices. Experts were significantly more likely to choose these treatments than non-experts in all scenarios ($p<0.001$ and odds ratios = 2.0, 2.3 and 2.3, respectively). Significant interactions were observed between expert and scenario for IV immunoglobulin ($p<0.001$) and cyclophosphamide ($p=0.007$) with the nature of the interaction terms suggesting that experts use these more powerful and expensive treatments selectively.

The influence of country of practice

As the number of responses from individual countries (except the UK) was generally low, responses were grouped into the following subgroups; UK, Europe excluding the UK, North America, South America, East Asia, Australia and India. Using these groupings there was a significant effect on first-line immunosuppressant choice dependent on geographical origin that persisted after allowing for expert status. For many agents there was also a significant interaction between expert and geographical subgroup, suggesting that in a location where a particular agent was more commonly chosen, experts were also more likely to prescribe that agent than experts in other countries where the agent was less commonly chosen. For example, for the first-line choice of IV Immunoglobulin there is a significant effect between countries ($p<0.001$) and this remains when allowing for expertise ($p<0.001$). Compared to the UK the likelihood of choosing IV Immunoglobulin first-line is significantly lower in Australia ($p=0.010$), Europe ($p=0.010$) and South America ($p=0.020$) but is significantly higher in North America ($p=0.006$). There is also a significant interaction ($p<0.001$) between the expert and country, suggesting that the difference in prescribing practice of experts and non-experts may vary in some locations.

Consistency of approach

In most scenarios the most popular treatment choice was selected by more than half of respondents. Scenario 5 showed the greatest degree of disparity between respondents: This was designed to be clinically indicative of inclusion body myositis but, as is often the case, with a suggestive but inconclusive muscle biopsy. In this context 76% of rheumatologists and 50% of neurologists felt pharmacotherapy was appropriate. For the neurologists electing to treat, this was restricted to oral prednisolone alone however 64% of treating rheumatologists would also recommend an additional immunosuppressive agent and some IV prednisolone. Disparity of treatment choices was also apparent in Scenario 6 (clinically amyopathic myositis and cutaneous features suggestive of anti-MDA5 autoantibodies), where the overall first-line immunosuppressant preferences were less apparent (supplementary Figure 1). Furthermore, the most popular choices included both drugs generally perceived as 'aggressive' (IV cyclophosphamide) 'moderately aggressive' (azathioprine, methotrexate and mycophenolate mofeti) and 'mild' (hydroxychloroquine) suggesting a lack of uniformity in approach.

Discussion

This study has several limitations including the limited responses from non-experts in countries other than the UK and Australia and the low number of responses from non-rheumatologists. The survey did not examine drug dosing nor treatment regimen *e.g.* induction versus maintenance therapy nor encompass all of the variability seen in IIM. Despite these limitations it is interesting to note that in most scenarios assessed, comparable treatments were suggested by survey respondents, despite the lack of a robust evidence base or treatment guidelines. While certain drugs appeared uniformly popular, namely azathioprine, methotrexate and mycophenolate mofetil, clinical scenario had a significant influence on prescribing choice. We assume this relates to the perceived risk of disease complications, such as interstitial lung disease, or the supposed likelihood of treatment response suggested by autoantibody status and/or other clinical features described. The reduced likelihood of prescribing methotrexate in scenarios 1 and 6 may be due to the suggestion of interstitial lung disease in both of these cases. In a recent systematic review of immunomodulatory treatment in polymyositis and dermatomyositis we noted that only two randomised controlled trials analysed the distribution of myositis-specific and myositis-associated autoantibodies between treatment groups, and the impact of the presence of various autoantibodies on outcome and treatment response was only assessed in one (2). Subgroup analyses such as these are particularly challenging in view of the rarity of myositis and international collaborations will be crucial in achieving this. Glucocorticoids plus an additional immunosuppressant was the most commonly selected treatment in most scenarios, despite a lack of evidence for the benefit of combination therapy in adult patients: The second line agents in myositis study, which compared steroids alone to steroids plus methotrexate, ciclosporin or both, failed to demonstrate a difference in intention to treat analyses or even to demonstrate a steroid sparing effect for combination therapy (7). Whilst these results call the continued use of these agents into question, patients enrolled in this study had active disease despite steroid therapy and, when the same agents were used in newly diagnosed juvenile patients the results clearly favoured combination treatment, and MTX had a better safety profile compared to CsA (8). Furthermore, the large, placebo controlled, rituximab in myositis study whilst failing to meet its endpoint was able to demonstrate a significant steroid sparing effect with the addition of rituximab (9).

Self-reported expertise also significantly influences immunosuppressant choice and interestingly experts select from a more limited range of drugs for first-line treatment and are more likely to choose the three most popular immu-

nosuppressants. Despite a lack of treatment guidelines experts also appear to modify their treatment approach in the same way in the different scenarios. The increased range of drugs used non-selectively by non-experts, particularly as these include more expensive and potentially toxic treatments, highlights the need for clear treatment recommendations in addition to the potential benefits of expert involvement in the care of these rare and difficult diseases.

Disparities in prescribing choice were most apparent in two scenarios, scenario 5 and scenario 6. We speculate that in scenario 5 (inclusion body myositis) the high rate of respondents recommending treatment reflects a desire to try 'something' that may help, in addition to a lack of diagnostic certainty, as no therapy has to date been shown to alter the course of this disease (10). In scenario 6 (clinically amyopathic myositis and cutaneous features suggestive of anti-MDA5 autoantibodies) respondents appear to be split into two camps; those treating aggressively and those with a more conservative approach. We hypothesise that this reflects the real-life difficulty of recognising patients prone to clinically significant complications, such as interstitial lung disease as in this case, in the absence of readily available autoantibody testing.

In every-day practice treatment choices are influenced not only by physician experience and preferences but also by the availability of resources and cost. This may explain the differences in prescribing choice by location of practice, particularly if national prescribing restrictions are in place for some medications. While we are unable to determine the influence of cost and availability of immunosuppressant options in the minds of the respondents, the popularity of more affordable, generic medicines looks promising for the development of international consensus guidelines that can be widely applied.

Conclusion

Comparable treatments were suggested by most respondents despite a lack of evidence and guidelines. Pharmacological treatment with steroids and additional immunotherapy is the preferred treatment for most patients with IIM. First-line immunosuppressant choice is influenced by clinical phenotype and the expertise and origin of the treating physician. In the absence of available evidence, clinical experience and expert consensus often forms the basis of treatment guidelines. This survey suggests that in IIM such an international consensus approach would be possible.

Acknowledgements

The authors are grateful to all those who completed the survey, to IMACS members who initiated the concept for the study and aided in its development, and to those who aided in its distribution, including the Bath Institute for Rheumatic Diseases, IMACS, EUMyoNet, UKMyoNet and the British Society of Rheumatology.

References

1. TANSLEY SL, MCHUGH NJ: Myositis specific and associated autoantibodies in the diagnosis and management of juvenile and adult idiopathic inflammatory myopathies. *Curr Rheumatol Rep* 2014; 16: 464.
2. VERMAAK E, TANSLEY S, MCHUGH N: The evidence for immunotherapy in dermatomyositis and polymyositis: a systematic review. *Clin Rheumatol* 2015: 1-7.
3. GORDON PA, WINER JB, HOOGENDIJK JE, CHOY EH: Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis. *Cochrane Database Syst Rev* 2012; 8: CD003643.
4. BARSOTTI S, TERENZI R, LA PAGLIA GM, BELLUCCI E, BALDINI C, NERI R: One year in review 2015: idiopathic inflammatory myopathies. *Clin Exp Rheumatol* 2015; 33: 593-601.
5. AGGARWAL R, BANDOS A, REED AM *et al*.: Predictors of clinical improvement in rituximab-treated refractory adult and juvenile Dermatomyositis and adult polymyositis. A*rthritis Rheumatol* 2014; 66: 740-9.
6. TEAM RC: R Foundation for Statistical Computing Vienna, Austria 2012.
7. IBRAHIM F, CHOY E, GORDON P *et al*.: Second-line agents in myositis: 1-year factorial trial of additional immunosuppression in patients who have partially responded to steroids. *Rheumatology* (Oxford) 2015; 54: 1050-5.
8. RUPERTO N, PISTORIO A, OLIVEIRA S *et al*.: Prednisone versus prednisone plus ciclosporin versus prednisone plus methotrexate in new-onset juvenile dermatomyositis: a randomised trial. *Lancet* 2015.
9. ODDIS CV, REED AM, AGGARWAL R *et al*.: Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: A randomized, placebo-phase trial. *Arthritis Rheum* 2013; 65: 314-24.
10. ROSE MR, JONES K, LEONG K *et al*.: Treatment for inclusion body myositis. *Cochrane Database Syst Rev* 2015; CD001555.