Quantitative muscle magnetic resonance imaging as a biomarker for inclusion body myositis in clinical trials: exploring the *in vivo* effects of arimoclomol

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Abstract

Objective

To investigate the intramuscular effects of arimoclomol using quantitative magnetic resonance imaging (qMRI) of the thighs in a subset of inclusion body myositis (IBM) participants from a multicentre, randomised, double-blind, placebo-controlled trial, and to further evaluate the utility of qMRI assessments as outcome measures.

Methods

Eighteen participants (10 placebo, 8 arimoclomol-treated) were recruited to undergo an MRI at baseline, 12 and 20 months. Spearman correlations between baseline clinical measures and qMRI measurements [fat fraction (FF), remaining muscle area (RMA), magnetisation transfer ratio (MTR), muscle water T2 (T2m) and fat fraction apparent (FFa)] were used to evaluate construct validity. A mixed model repeated measures (MMRM) strategy was employed to estimate mean changes, in order to determine treatment effects on qMRI biomarkers and evaluate responsiveness to disease progression over time. Longitudinal analyses examined Spearman correlations between changes in qMRI and changes in clinical assessments at the last available follow-up.

Results

Baseline FF, RMA, MTR and FFa of the thigh and quadriceps demonstrated strong construct validity. No significant treatment effects on the qMRI measures were detected. FF, RMA and FFa demonstrated strong responsiveness to disease progression (standardised response means>0.8, $p<0.05$) at 20 months. Longitudinal changes in thigh T2m were strongly correlated with changes in myometry and modified timed up and go velocity.

Conclusion

Arimoclomol had no significant effects on the qMRI measurements evaluated, consistent with clinical outcomes from the main trial. The qMRI measurements demonstrated both validity and responsiveness, further supporting their potential utility as biomarkers in IBM.

Key words

inclusion body myositis, biomarker, magnetic resonance imaging, thigh, clinical trial

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Competing interests: see page 343.

Introduction

Inclusion body myositis (IBM) is progressive condition belonging to the spectrum of idiopathic inflammatory myopathies (IIMs) (1-3). IBM often presents in middle age with the classical features of finger flexor, quadriceps and ankle dorsiflexor weakness. Infiltration of the endomysium by $CD8^+$ T-lymphocytes is a key histopathological feature for IBM (4). However, the predominant histopathological hallmarks are the downstream sequelae of aberrant aggregation including the rimmed vacuoles, sequestosome-1/p62 inclusions and TAR DNA-binding protein 43 (TDP-43) translocation from the nucleus to the cytoplasm (5). There are currently no treatments for IBM with a robust evidence base (6). Unlike the majority of IIMs, IBM does not respond to conventional avenues of immunosuppression. Therefore, a recent focus in research has been to target degenerative processes in IBM.

Arimoclomol is a drug that has previously been shown to upregulate the heat shock response and boost autophagy of intracellular proteins. Arimoclomol had initially shown promising results in experimental models of IBM (7). *In vitro* models using rat myoblast cultures demonstrated improvements in endoplasmic reticulum stress, protein aggregation and other histopathological changes including reduced inflammation. In a murine model using Valosin Containing Protein (VCP) mutant mice, administering arimoclomol improved intramuscular pathological changes and hind-limb strength. A larger randomised, double-blind, placebo controlled trial of arimoclomol was unable to demonstrate a beneficial treatment effect on the primary outcome variable of the change in the IBM functional rating scale (IBMFRS) total score over 20 months (8). A subset of IBM participants from this trial underwent magnetic resonance imaging (MRI) of the thigh. Despite the trial outcome, given the findings from initial pre-clinical models it was prudent to determine if there was evidence that arimoclomol modulated intramuscular changes in IBM participants.

Quantitative MRI (qMRI) measurements such as Dixon derived fat fraction (FF) and magnetisation transfer ratio (MTR) have been shown to correlate with other clinical outcome measures including IBMFRS total score, six-minute walk test (6MWT) distance, and manual muscle testing (MMT) grading (9-12). FF of the lower limb muscles has been shown to increase longitudinally over the course of one year in IBM participants (10, 12). qMRI measures such as FF have been shown to be valid and responsive markers of disease that could be used as outcome measures in clinical trials (10, 12, 13). In addition, functioning remaining muscle area (RMA), which is derived using FF, has been shown to be a responsive measure of disease in IBM. (12) RMA of quadriceps has been associated with myometric knee strength in IBM patients; both cross-sectionally and longitudinally (12).

The primary objective of this study was to investigate arimoclomol's impact on thigh FF after 20 months of treatment. As secondary objectives, the treatment effects on a variety of other qMRI measures were examined, including changes in the quadriceps muscle only. Furthermore, this study aimed to further explore the utility of qMRI as a clinical outcome measure in IBM patients.

Methods

Study participants

The trial included 150 randomised participants, 73 in the arimoclomol group and 77 in the placebo group. As outlined by Machado *et al*., treated participants received arimoclomol 400mg three times a day for the entire trial length of 20 months.(8) Two sites participated in the MRI study: National Hospital for Neurology and Neurosurgery (NHNN), London, UK, and Kansas University Medical Centre (KUMC), Kansas, USA. The MRI study was an optional component of the trial, and 18 participants were recruited to undergo MRI assessments of the thigh at baseline, 12 months and 20 months.

Ethics approval

This study involves human participants and the Arimoclomol trial study protocol was approved by the relevant Institutional Review Board (IRB)/Research Ethics Committee (REC), using a single IRB

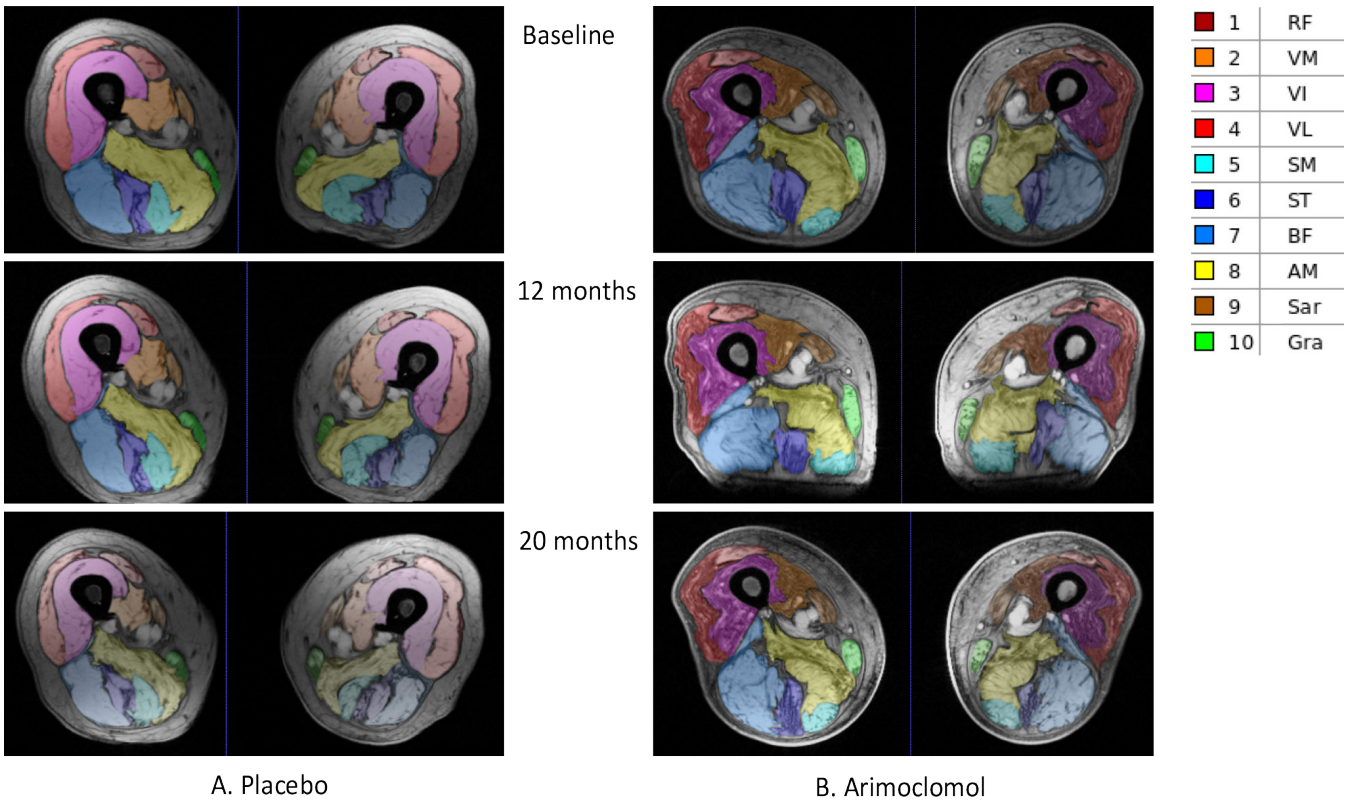

Fig. 1. Examples of thigh muscle ROIs delineated for the arimoclomol MRI study. Thigh ROI examples from a placebo-treated patient (**A**) and an arimoclomol-treated patient (**B**). Serial imaging performed at baseline, 12 months and 20 months. Key for thigh muscles segmented: 1. RF: Rectus Femoris (Maroon); 2. VM: Vastus Medialis (Orange); 3. VI: Vastus Intermedius (Purple); 4. VL: Vastus Lateralis (Red): 5. SM: Semimembranosus (Turquoise); 6. ST: Semitendinosus (Dark blue); 7. BF: Biceps femoris (Light blue); 8. AM: Adductor Magnus (Yellow); 9. Sar; Sartorius (Brown): 10. Gra: Gracilis (Green).

review via the SMART IRB platform for the 11 US centres (University of Kansas Medical Center Human Research Protection Program, reference number STUDY00002461) and the Health Research Authority (HRA) approval process for the UK centre (London - Surrey Borders Research Ethics Committee, reference number: 18/LO/0696). The trial is registered with ClinicalTrials.gov, number NCT02753530 and is completed. The trial was conducted in accordance with the Declaration of Helsinki (October 2013) and its revisions as well as with the valid national laws of the participating countries and the Integrated Addendum to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ICH E6(R1): Guideline for Good Clinical Practice (GCP) E6 (R2) effective 14 June 2017, European Regulation No. 536/2014 and with the Commission Directives 1991/507/EEC and 2001/83/EC. Participants gave informed consent to participate in the study before taking part.

Clinical assessments

Study participants underwent regular assessments following the trial schedule over 20 months. For the purposes of this study, outcomes obtained at baseline, 12 months and 20 months, corresponding to the MRI assessment timepoints, were used.

The IBMFRS total score was obtained at each timepoint.(14-17) In addition, an IBMFRS lower limb score was calculated using three items focusing on lower limb function (sit to stand, walking and climbing stairs). MMT score was obtained at each timepoint and for the purposes of this study, the knee extension score was used. Myometric knee extensor strength was examined using the MicroFET hand-held dynamometer device (Hoggan Health Industries, Salt Lake City, UT, USA). In addition, timed measures of ambulatory function including 6MWT distance and modified timed up and go (mTUG) were obtained. When analysing the mTUG, the reciprocal value of the measured time multiplied by the planned total distance of 6 metres was used. This corresponds to analysing the velocity of the walking speed expressed in meters per second (m/s), including the time spent for standing up and sitting down again, and allowed the adoption of the value "zero" for participants unable to perform the assessment.

MRI acquisition

MRI assessment of the thighs was performed at baseline, 12 months, and 20 months, with a 4-week window for each MRI. UK participants were examined within a 3T MRI scanner (Prisma, Siemens, Erlangen, Germany) at the NHNN. US participants were scanned in the same position within a 3T MRI scanner (Skyra, Siemens, Erlangen, Germany) at the KUMC. MRI procedures employed were identical at both participating sites.

Quantitative FF maps of the thigh were generated from 3-point Dixon images (2D gradient echo, ten 10 mm slices, TR=101 milliseconds (ms), TE=3.45/4.60/5.75 ms, flip-angle=10

degrees, NSA=4, FOV=410, voxel size 0.8×0.8×10.0 mm^3). MTR maps were acquired using 3D FLASH sequences both with and without MTC (forty 5 mm slices, TR=68 ms, TE=3 ms, flip-angle=10 degrees, NSA=1, FOV=410, voxel size 1.6×1.6×5.0 mm^3). T2 relaxometry maps were produced with a multi-echo-spin-echo sequence (five 6 mm slices, TR=3500 ms, TE=10, 22 echoes to 220 ms in 10 ms steps, flip angle = 180 degrees, NSA=1, FOV=420mm, voxel size 1.3 x 1.3 x 6 mm^3).

MRI analysis

Ten thigh muscles were delineated as regions of interest (ROIs) using the ITKSNAP program (Fig. 1) (18). ROIs were drawn by an assessor who had completed a local training program for lower limb muscle anatomic segmentation upon a raw 3-point Dixon source image (19). The ROIs underwent rigorous quality control, including a selection of cases also being reviewed by another experienced reader. ROIs were drawn in a comparable mid-thigh slice for all participants, at the slice most closest to 200 mm from the lateral tibial plateau. As previously outlined, ROIs were used to extract summary statistics from the quantitative MRI parameter maps, directly for the inherently co-registered FF maps, and following any necessary minor adjustments to co-register the ROIs to the MTR maps (12). Fat fraction maps overlaying the defined ROIs were used to calculate FF (12). The cross-sectional area (CSA) of the individual muscles were also calculated and used to derive the RMA using the formula CSA x [(100-FF)/100].

T2 Maps were used to generate measures of fat fraction apparent (FFa) and T2 muscle water (T2m) using the multi-echo spin-echo data above mentioned and the Dixon data based anatomical segmentations which were adapted to the raw T_2 weighted images using a custom-written MATLAB tool. A multi-component (corresponding to the fat and muscle tissue compartments) slice profile- corrected EPG model [$s(TE) = (1 — FFa) \cdot sEPG(B_1f, T2m, \alpha, \sigma_N, TE) + FFa \cdot [0.33 \cdot sEPG(B_1f, T_2 = 40\ ms, \alpha, \sigma_N, TE) + 0.67 \cdot sEPG(B_1f, T_2 = 198\ ms, \alpha, \sigma_N, TE)]$] was fitted pixel-wise to the data using maximum likelihood estimation (MLE) in a custom-written MATLAB tool, to estimate T2m, the B_1 field error factor (B_1f), FFa, overall amplitude (α) and Rician noise SD (σ_N). The fixed 2-component fat signal model parameters were determined in a preliminary calibration as mean values estimated from 4 subcutaneous fat ROIs in 8 representative subjects. Corrections were applied to FFa for magnetisation transfer and T_1 effects. For quality control, pixel values were excluded which failed to meet fit- quality criteria [R^2 (goodness of fit) >0.8, and T2m>10 ms] or appeared as pure fat (T2m<15 ms & FFa>90%).

Weighted means (according to the volume of each corresponding ROI) were calculated for FF, MTR, FFa and T2m values of the entire (mean of right and left sides) thigh or quadriceps, and right and left sides separately.

Statistical analysis

Statistical analyses were performed using SPSS (Version 29). Spearman rank correlation coefficients were used to quantify the associations between qMRI measures and clinical measures, and also between changes in these.

Correlations were assessed in line with Cohen's recommendations whereby correlations were considered weak if the resulting coefficient was <0.3; moderate if between 0.3 and <0.5; and strong if ≥0.5.(20) Similarly when assessing the degree of responsiveness to disease progression, standardised response means (SRMs) between 0.2 and <0.5 was considered small; medium if between 0.5 and <0.8; and large if ≥0.8. When assessing statistical significance of correlations and mean change, two-tailed *p*-values were utilised.

We implemented a similar mixed model repeated measures (MMRM) approach to that in the main trial in order to estimate the treatment effect of arimoclomol and investigate responsiveness of the qMRI measures at 20 months (8). Specifically, this approach included all observed changes from baseline to Months 12 and 20, with treatment group, month (categorical variable), and the interaction between treatment group and month included in the model. An unstructured covariance matrix was used to model dependence of the qMRI measurements within the same participant. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom (21). This model was used to estimate the adjusted group mean change from baseline at Month 20, as well as the treatment group difference in adjusted group means at Month 20 along with its associated 95%

Table I. Clinical and demographic characteristics of the MRI study cohort.

Male, n, (%)	13 (72.2)
Age, years, mean (SD)	66.3 (8.5)
Received arimoclomol, n (%)	8 (44.4)
Anti-cN1A seropositivity, n (%)	5 (27.7)
IBMFRS total score, mean (SD)	27.9 (4.3)
IBMFRS lower limb score, mean (SD)	6.4 (2.1)
Knee extension MMT score, mean (SD)	6.5 (2.5)
Knee extension myometry, kilograms, mean (SD)	10.5 (6.0)
6MWT, m, mean (SD)	319.2 (90.7)
mTUG, m/s, mean (SD)	0.49 (0.18)
Thigh FF, %, mean (SD)	25.1 (17.5)
RMA, cm^2, mean (SD)	121.9 (50.6)
Thigh MTR, %, mean (SD)	21.2 (5.7)
Thigh FFa, %, mean (SD)	38.0 (16.1)
Thigh T2m, ms, mean (SD)	36.7 (4.4)
MRI scan available, n (%)	
Baseline	18 (100)
12 months	9 (50)
20 months	9 (50)
All time points	5 (27.8)

cN1A: cytosolic 5'-nucleotidase 1A; FF: fat fraction; FFa: fat fraction apparent; IBMFRS: Inclusion Body Myositis Functional Rating Scale; MMT: Manual Muscle Testing; mTUG: modified Timed Up and Go velocity; MTR: magnetisation transfer ratio; SD: standard deviation; T2: T2 muscle water; 6MWT: 6-minute walk test distance.

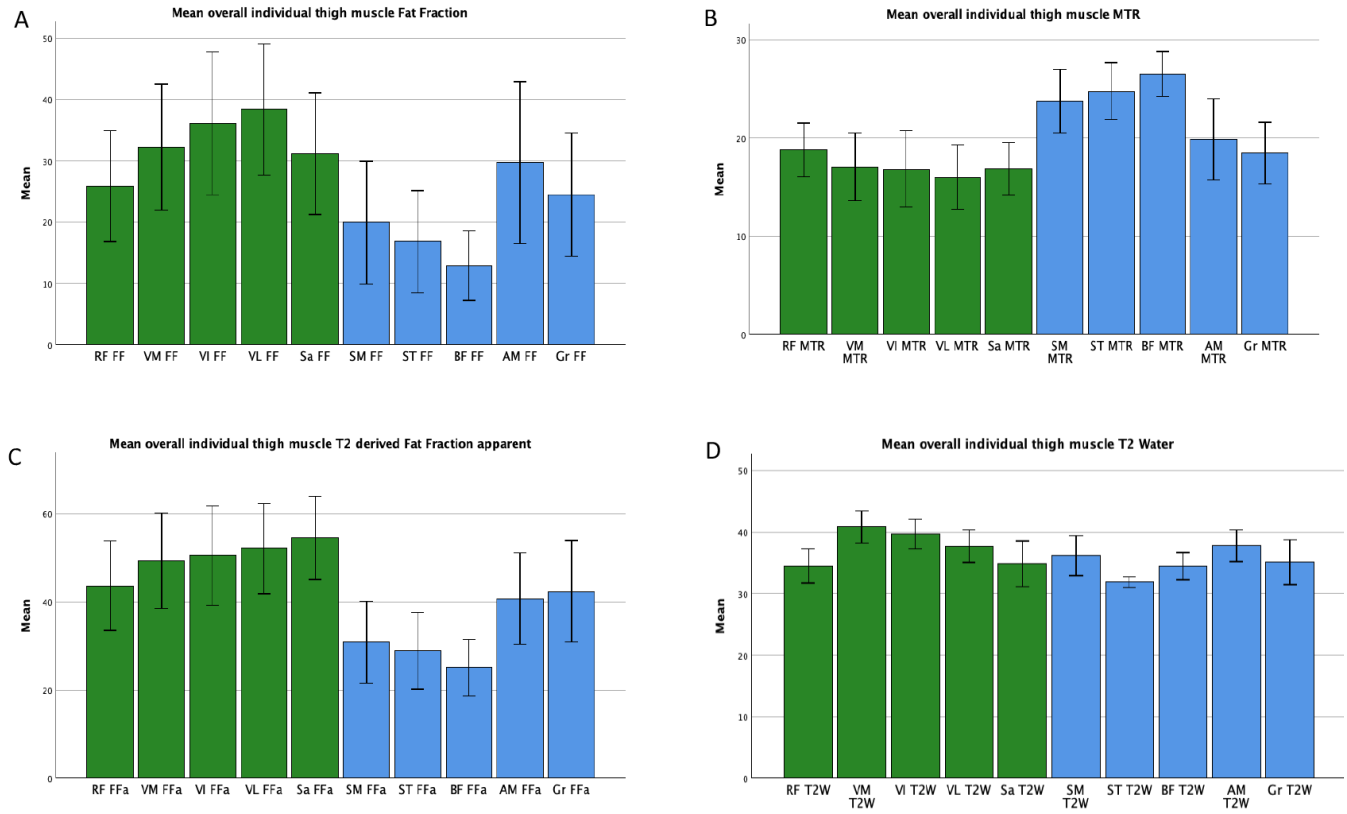

Fig. 2. Imaging pattern of individual thigh muscle involvement at baseline (n=18). Green bars represent anterior thigh compartment muscles and blue bars represent posterior thigh compartment muscles, error bars representing standard deviation.
FF: fat fraction; MTR: magnetisation transfer ratio; FFa: fat fraction apparent; RF: rectus femoris: VM: vastus medialis; VI: vastus intermedius; VL: vastus lateralis: Sa: sartorius, SM: semimembranosus; ST: semitendinosus; BF: biceps femoris: AM: adductor magnus; Gr: gracillis.

confidence interval and *p*-value. It also accommodated missing data under the missing at random assumption. A similar model was used to estimate the overall mean change from baseline to Month 20, with only month (12, 20) included in the model. The Standardised Response Mean (SRM) was estimated as the mean change from baseline to Month 20 divided by the square root of the estimated variance component for Month 20.

Results

The mean age of participants in this study was 66.3 years and there was a male preponderance (at a ratio of 13:5) (Table I). Five participants (27.7%) tested positive for anti-cN1A antibodies. Eight participants were in the arimoclomol arm of the trial and 10 were on the placebo arm.

In total, 18 IBM participants had qMRI of the thigh muscles at baseline. Only five participants had scans at all three time points, and three of these participants were on the arimoclomol arm. Nine participants were scanned at 12 months, and nine participants at 20 months. Of all the participants who had a baseline scan, 13 had a follow-up scan at either 12 or 20 months.

Imaging pattern of individual thigh muscle involvement at baseline

Fat infiltration was more pronounced in the anterior thigh than in the thigh posterior muscle compartments, especially the vastus muscles (Fig. 2). FF and FFa demonstrated fairly concordant findings when comparing both compartments. As expected, MTR values had a reciprocal appearance to FF. T2m of the thigh muscles appeared to be similar in both the anterior and posterior compartments.

Construct validity: baseline associations between qMRI measures and clinical outcome assessments

The correlations between qMRI measures of the whole thigh and other clinical assessments obtained during baseline visits were explored (Table II).

The strongest associations in the thigh were observed between MMT score and FF (r=-0.75, $p<0.001$), MTR (r=0.76, $p<0.001$) and FFa (r=-0.78, $p<0.001$). RMA of whole thigh overall demonstrated moderate to strong relationships with all clinical measures, although this was to varying degrees of strength of association. The strongest associations were with myometric knee extension (r=0.63, $p=0.005$) and mTUG (r=-0.59, $p=0.009$). Myometric knee extension score was also strongly associated with whole thigh FF (r=-0.51, $p=0.03$). Relaxometry derived FFa of the whole thigh and Dixon derived FF demonstrated similar associations with the clinical measures. FF, MTR, RMA and FFa all demonstrated strong associations with the mTUG. Overall, of all thigh qMRI measures explored, T2m had weaker correlations with the clinical outcome assessments. Moderate associations were seen between thigh T2m and 6MWT distance (r=- 0.49, p=0.04), IBMFRS total score and IBMFRS lower limb score. (Table II). The clinical measure that appeared

Table II. Correlations of qMRI measures of thigh and quadriceps with clinical outcome measures at baseline (n=18).

		IBMFRS Lower limb total score	IBMFRS total score	Knee extension MMT	Knee extension myometry (kg)	mTUG (m/s)	6MWT (m)
Thigh FF (%)	r	-0.23	-0.28	-0.75**	-0.51*	-0.57*	-0.36
	p-value	0.368	0.259	**<0.001**	**0.033**	**0.013**	0.140
Thigh RMA (cm^2)	r	0.48*	0.48*	0.47*	0.63*	0.59**	0.49*
	p-value	**0.043**	**0.045**	**0.049**	**0.005**	**0.009**	**0.039**
Thigh MTR (%)	r	0.25	0.33	0.76**	0.47*	0.59**	0.36
	p-value	0.30	0.187	**<0.001**	**0.047**	**0.009**	0.142
Thigh FFa (%)	r	-0.28	-0.37	-0.78**	-0.50*	-0.52*	-0.40
	p-value	0.257	0.135	**<0.001**	**0.035**	**0.026**	0.103
Thigh T2m (ms)	r	-0.41	-0.47	-0.29	-0.21	-0.42	-0.49*
	p-value	0.092	0.050	0.239	0.399	0.086	**0.040**
Quads FF (%)	r	-0.14	-0.24	-0.61*	-0.55*	-0.53*	-0.42
	p-value	0.580	0.335	**0.007**	**0.018**	**0.025**	0.086
Quads RMA (cm^2)	r	0.19	0.21	0.50*	0.71**	-0.37	0.28
	p-value	0.441	0.393	**0.034**	**<0.001**	0.132	0.265
Quads MTR (%)	r	0.30	0.42	0.75**	0.61*	0.69*	0.490*
	p-value	0.223	0.083	**<0.001**	**0.007**	**0.002**	**0.039**
Quads FFa (%)	r	-0.24	-0.35	-0.78**	-0.64*	-0.58*	-0.44
	p-value	0.330	0.160	**<0.001**	**0.004**	**0.012**	0.069
Quads T2m (ms)	r	0.44	-0.55*	-0.23	-0.22	0.39	-0.37
	p-value	0.071	**0.019**	0.359	0.372	0.106	0.128

Dark grey highlights represent strong correlations. Light grey highlights represent moderate correlations.
FF: fat fraction; FFa: fat fraction apparent; IBMFRS: Inclusion Body Myositis Functional Rating Scale; MMT: Manual Muscle Testing; mTUG: modified Timed Up and Go velocity; MTR: magnetisation transfer ratio; Quads: quadriceps; T2m: T2 muscle water; 6MWT: 6-minute walk test distance.

Table III. Estimated group mean changes in thigh and quadriceps qMRI measures.

qMRI measure	Placebo estimated mean change at 20 months (95% CI)	Arimoclomol estimated mean change at 20 months (95% CI)	Difference in estimated mean change at 20 months (95% CI)	*p*-value
Thigh FF (%)	3.14 (-1.14 to 7.42)	5.27 (0.21 to 10.32)	2.13 (-4.49 to 8.75)	0.49
Thigh RMA (cm^2)	-18.74 (-35.23 to -2.25)	-12.84 (-28.96 to 3.28)	5.90 (-17.14 to 28.93)	0.56
Thigh MTR (%)	-0.62 (-3.28 to 2.04)	-0.91 (-3.26 to 1.44)	-0.29 (-3.83 to 3.25)	0.85
Thigh FFa (%)	4.07 (0.22 to 7.92)	3.18 (-0.78 to 7.15)	-0.89 (-6.41 to 4.64)	0.73
Thigh T2m (ms)	0.43 (-1.52 to 2.34)	0.61 (-1.11 to 2.34)	0.19 (-2.42 to 2.79)	0.87
Quads FF (%)	4.39 (-0.41 to 9.19)	4.65 (-0.67 to 9.97)	0.26 (-6.89 to 7.42)	0.93
Quads RMA (cm^2)	-6.86 (-14.39 to 0.68)	-6.08 (-13.55 to 1.39)	0.77 (-9.82 to 11.36)	0.87
Quads MTR (%)	-1.20 (-4.11 to 1.70)	-1.68 (-4.12 to 0.76)	-0.47 (-4.25 to 3.30)	0.77
Quads FFa (%)	4.48 (-0.64 to 9.60)	3.94 (-0.79 to 8.67)	-0.53 (-7.49 to 6.42)	0.87
Quads T2m (ms)	1.11 (-2.34 to 4.57)	0.99 (-2.29 to 4.28)	-0.12 (-4.88 to 4.64)	0.96

FF: fat fraction; FFa: fat fraction apparent; IBMFRS: Inclusion Body Myositis Functional Rating Scale; MMT: Manual Muscle Testing; Quad: quadriceps; T2m: T2 muscle water.

to have the weakest associations with the thigh qMRI measures was the IBMFRS lower limb score. The correlations between qMRI assessments of the right and left thigh in isolation and knee extension MMT and myometry were similar to those that used the mean of the right and left thigh measurements (Supplementary Table S1).

The relationships between the qMRI investigations of the overall quadriceps muscles (mean of right and left quadriceps grouped together) and clinical assessments were also explored (Table II). The findings were generally similar to those of qMRI assessments of the thigh. However, MTR of the combined quadriceps muscles appeared to have more consistent construct validity; moderate to large correlations were noted with all clinical measures. MMT and myometric assessments of knee extension were the clinical measures which had the strongest associations with the qMRI measures of the quadriceps. Again the strongest association in the quadriceps was observed between FFa and knee extenstion MMT (r =-0.78, $p<0.001$).

The correlation between qMRI assessments of the right and left quadriceps in isolation with knee extension MMT and myometry was also evaluated

(Suppl. Table S2). RMA of the quadriceps muscles strongly correlated with myometric knee extension bilaterally, left (r=0.55, *p*=0.019) and right (r=0.69, *p*=0.001). As observed in the associations between the individual thigh qMRI measures and knee extension assessments (Suppl. Table S1), qMRI measures of the right quadriceps correlated better with myometry than those of the left quadriceps. Except for the left quadriceps RMA, no left-sided thigh or quadriceps qMRI measurements achieved a strong correlation with left knee extension myometry.

The correlations between each of the individual muscles comprising the quadriceps and the corresponding right and left knee extension strength measures were examined (Suppl. Tables S3 and S4). These findings were consistent with those observed in the grouped right and left quadricep muscles MRI assessments (Suppl. Table S2). Apart from the right vastus intermedialis, the remaining quadriceps T2m values did not exhibit any moderate or strong correlations with knee extension strength measures.

Treatment effects of arimoclomol on qMRI measures

Both the placebo and arimoclomol treated groups showed a mean increase in FF of the overall thigh after 20 months. The difference in the estimated mean change in overall thigh FF at 20 months between arimolcomol and placebo was not statistically significant (difference in estimated mean 2.13, 95% CI -4.49 to 8.75, *p*=0.49). Similarly, there were no statistically significant intervention effects on other thigh qMRI assessments (Table III). Furthermore, no significant treatment effects were observed on quadriceps qMRI measurements (Table III).

Responsiveness of qMRI measures

The responsiveness of the qMRI measurements at the end of the trial (Month 20) is summarised in Table IV. Overall thigh FF, RMA and FFa demonstrated large SRMs, whereas thigh MTR and T2m assessments achieved smaller degrees of responsiveness.

To provide more granularity, the responsiveness of the qMRI assessments of the quadriceps was investigated. In general, the qMRI measurements of the quadriceps behaved similarly to those of the overall thigh. Again FF, RMA and FFa of the quadriceps achieved high responsiveness. Quadriceps MTR tended to perform better than the overall thigh MTR, achieving a medium responsiveness (SRM=0.74).

At both the thigh and quadriceps levels, RMA demonstrated the strongest responsiveness of all qMRI measures assessed (SRMs >1). All thigh and quadriceps qMRI assessments achieving a large SRMs were accompanied with statistically significant estimated mean changes. Mean change in thigh FFa achieving the highest degree of significance (3.66, *p*=0.009).

Correlations between changes in qMRI measures and changes in clinical measures at the last available follow-up visit (Month 12 or Month 20)

When evaluating longitudinal changes in qMRI measures, we pooled assessments obtained at the last available follow up, either 12 months (n=3) or 20 months (n=9) (Table V).

The strongest longitudinal association at the thigh level was between the change in thigh T2m and change in myometry at the last follow up (r=-0.70, *p*=0.017). The second strongest correlation was that between the longitudinal change in thigh T2m *versus* change in mTUG; (r=-0.65, *p*=0.043). Longitudinal change in thigh RMA had two associations which achieved strong Spearman coefficients: with changes in IBMFRS (r=0.51, *p*=0.092) and 6MWT (r=0.60, *p*=0.067). A number of moderate correlations were observed in the longitudinal changes in qMRI thigh assessments and changes in clinical outcome measures.

Finally, longitudinal changes in the qMRI measurements of quadriceps at the last follow-up was investigated. Again, change in quadriceps T2m achieved a strong correlation with change in knee extension myometry (r=-0.66, *p*=0.028) and the change in mTUG, (r=-0.53, *p*=0.117). A few moderate correlations were also observed between longitudinal changes in qMRI quadriceps assessments and changes in clinical measures.

Table IV. Responsiveness statistics for thigh and quadriceps qMRI measures at 20 months.

qMRI measures	Estimated mean change (SD)	t value at 20 months	*p*-value	SRM
Thigh FF (%)	4.43 (4.65)	2.92	**0.015***	0.95
Thigh RMA (cm^2)	-15.58 (13.04)	-3.32	**0.012***	-1.19
Thigh MTR (%)	-0.78 (2.18)	-1.1	0.301	-0.36
Thigh FFa (%)	3.66 (4.15)	3.08	**0.009***	0.88
Thigh T2m (ms)	0.56 (1.53)	1.08	0.310	0.36
Quads FF (%)	4.46 (4.59)	2.63	**0.034***	0.97
Quads RMA (cm^2)	-6.36 (6.19)	-2.91	**0.019***	-1.03
Quads MTR (%)	-1.47 (1.99)	-1.98	0.083	-0.74
Quads FFa (%)	4.13 (4.62)	2.89	**0.015***	0.89
Quads T2m (ms)	1.15 (3.24)	1.15	0.273	0.35

Dark grey highlights represent large SRMs. Light grey highlights represent medium SRMs.
FF: fat fraction; FFa: fat fraction apparent; IBMFRS: Inclusion Body Myositis Functional Rating Scale; MMT: Manual Muscle Testing; Quads: quadriceps; SD: standard deviation; SRM: standardised response mean; T2m: T2 muscle water.
p-values demonstrated for estimated mean changes.

Discussion

In this study, we used qMRI to explore *in vivo* changes of the thigh muscles within a subset of participants in a recent clinical trial investigating the efficacy of arimoclomol (8). We further examined the utility of qMRI assessments as outcome measures using data from an actual clinical trial, a scenario in which outcome measure performance is most relevant. This is the first study to our knowledge that has prospectively investigated qMRI changes in a group of IBM participants beyond 12 months. Our group has previously investigated the use of Dixon derived FF, MTR and T2 relaxation time in lower limb muscles (10, 12). We also explored FFa and

Table V. Associations between changes in qMRI measures of thigh and quadriceps and changes in clinical outcome measures at the last available follow-up visit (Month 12 or Month 20).

		Change in IBMFRS lower limb total scores	Change in IBMFRS total score	Change in mean knee extension MMT	Change in mean knee extension myometry (kg)	Change in mTUG (m/s)	Change in 6MWT (m)
Change in thigh FF (%)	r	0.11	-0.02	-0.35	-0.27	-0.38	-0.19
	p-value	0.731	0.948	0.297	0.444	0.308	0.603
	n	12	12	11	10	9	10
Change in thigh RMA (cm²)	r	0.17	0.51	0.47	-0.21	0.47	0.60
	p-value	0.605	0.092	0.145	0.567	0.205	0.067
	n	12	12	11	10	9	10
Change in thigh MTR (%)	r	0.46	-0.03	-0.29	0.09	0.12	-0.02
	p-value	0.115	0.928	0.358	0.800	0.751	0.958
	n	13	13	12	11	10	11
Change in thigh FFa (%)	r	-0.09	-0.15	-0.33	-0.22	-0.37	-0.25
	p-value	0.782	0.615	0.301	0.518	0.293	0.467
	n	13	13	12	11	10	11
Change in thigh T2m (ms)	r	-0.36	-0.22	-0.23	-0.70*	-0.65*	-0.38
	p-value	0.229	0.478	0.483	**0.017**	**0.043**	0.259
	n	13	13	12	11	10	11
Change in quads FF (%)	r	0.16	-0.20	-0.23	-0.22	.013	0.22
	p-value	0.629	0.543	0.0501	0.544	0.732	0.533
	n	12	12	11	10	9	10
Change in quads RMA (cm²)	r	-0.14	0.37	0.36	-0.07	-0.05	0.20
	p-value	0.654	0.242	0.270	0.841	0.898	0.580
	n	12	12	11	10	9	10
Change in quads MTR (%)	r	0.07	-0.23	-0.35	-0.05	-0.38	-0.42
	p-value	0.834	0.450	0.258	0.894	0.276	0.201
	n	13	13	12	11	10	11
Change in quads FFa (%)	r	0.02	0.03	-0.23	-0.19	0.06	0.06
	p-value	0.947	0.928	0.483	0.582	0.881	0.873
	n	13	13	12	11	10	11
Change in quads T2m (ms)	r	-0.07	0.22	-0.08	-0.66*	-0.53	-0.23
	p-value	0.826	0.473	0.803	**0.028**	0.117	0.502
	n	13	13	12	11	10	11

Dark grey highlights represent strong correlations. Light grey highlights represent moderate correlations.
FF: fat fraction; FFa: fat fraction apparent; IBMFRS: Inclusion Body Myositis Functional Rating Scale; MMT: Manual Muscle Testing; mTUG: modified Timed Up and Go velocity; MTR: magnetisation transfer ratio; Quads: quadriceps; T2m: T2 muscle water; 6MWT: 6-minute walk test distance.

T2m in this study, which were derived from T2 relaxometry.

At baseline, the pattern of muscle fat infiltration was most pronounced in the anterior thigh muscles or quadriceps muscles which is what would be expected based on previous reports (10-12). T2m appeared to be similar in the anterior and posterior thigh muscle compartments.

Overall, the majority of baseline psychometric results were consistent with those reported in previous studies (9, 10, 12, 22). In particular, we found thigh RMA to have moderate to strong associations with all clinical measures explored in the study. Unlike previous reports, we were unable to demonstrate a significant association of whole thigh FF with IBMFRS total score or 6MWT distance (10, 13). When investigating qMRI measurements of the quadriceps we found similar observations to those with whole thigh qMRI. MTR appeared to demonstrate better construct validity at the quadriceps level, with a higher frequency of strong associations. MTR itself is a complex qMRI measure providing insight into the macromolecular structure of muscles (10, 12, 23). MTR is sensitive to relative changes in the populations of free water in tissue and the rate of magnetisation exchange from other proton pools. As the quadriceps appear to be more severely involved in IBM, macromolecular integrity of these muscles may be particularly worsened. Furthermore, the magnetisation transfer contrast of fat is fairly limited compared to healthy lean muscle. Therefore, MTR values in quadriceps could have also been influenced further by marked fat infiltration. Similar to previous investigations performed by our group, right and left quadriceps RMA exhibited strong correlations with knee extension myometry (10, 12). Knee extension MMT scores had strong relationships with the majority of FFa, FF, MTR and RMA assessments for the thigh and quadriceps bilaterally.

The associations between mTUG and qMRI measurements in IBM had not previously been investigated in the literature. We demonstrated mTUG velocity to have strong associations with all thigh qMRI variables investigated, apart from T2m.

At the end of trial (Month 20), there was no effect of arimoclomol that was detected on any of the qMRI measures investigated, though the sample size was quite small. These results are consistent with the absence of treatment effects on clinical measures in the main trial itself (8). At the time of this manuscript, only two other drug trials for IBM have explored the use of qMRI as an outcome assessment. The RESILIENT trial demonstrated that bimagrumab did not meet the primary endpoint of significantly halting, reducing deterioration, or improving 6MWT distance (24). Prior to this larger trial, a pilot study investigated the effects of bimagrumab using MRI (25). Amato *et al*. utilised qMRI to assess the effects of the drug in 11 patients compared to three placebo-treated patients. The authors were able to demonstrate a significant increase in total thigh muscle volumes in treated patients compared to the placebo group, but did not explore other qMRI measures. A phase 2b trial exploring the treatment effect of sirolimus in 40 IBM patients was also unable to detect a beneficial effect on the primary endpoint of isometric knee strength but did demonstrate treatment-associated benefit on a variety of secondary endpoints including an improvement in thigh FF (26). A more detailed investigation into the effects of sirolimus on qMRI measures of the lower limb was recently conducted by Reyngoudt *et al*. in this trial cohort (13). The authors demonstrated a significantly lower FF increase in the sirolimus-treated group after 1 year (0.7%), compared to the placebo group (3.2%). Moreover, RMA dropped to a lesser extent in participants receiving sirolimus.

Although most studies have explored responsiveness of qMRI biomarkers after approximately one year, this study has allowed us to explore responsiveness beyond this timeframe (9, 10, 12, 13, 27, 28). In particular RMA, FF and FFa demonstrated strong responsiveness in assessing thigh and quadriceps over 20 months.

We observed a number of moderate-to-large correlations between changes in qMRI indices and changes in clinical outcome measures at the last available follow-up visit. While T2m demonstrated comparatively weaker construct validity and responsiveness, of all the qMRI measures investigated T2m achieved the strongest longitudinal relationships. There has been some debate on the utility of T2 sequences in the context of IBM. Higher T2 signals in muscles have been shown to be associated with inflammation in biopsies taken from the same muscle (29). We have previously observed an increase in thigh T2 relaxation time over the course of a year in IBM patients (12). However, these global T2 relaxation times reflected a combined signal from both intramuscular fat and water content (10, 12, 30). In this study rather than utilising global T2, any T2 signals from fat accumulation were separated to provide the T2m parameter. Therefore T2m values allowed us to specifically estimate water accumulation within the thigh muscles (30). A recent study also investigated the use of T2m in IBM patients; demonstrating thigh T2m to significantly increase over the course of one year (22). The authors described significant negative associations between T2m and clinical measures such as the IBMFRS total score. Reyngoudt *et al*. also demonstrated T2m to be significantly higher in the quadriceps of IBM patients when compared to posterior thigh compartment (13). Longitudinal increases in T2m of the vastus lateralis were associated with a decline in 6MWT distance at one year in this cohort. T2m significantly increased in the sirolimus-treated group, perhaps secondary to muscle swelling induced by sirolimus itself. Conversely, we have also demonstrated a negative association between longitudinal change in global T2 relaxation time and fat deposition, indicating that fat deposition may be preceded by muscle inflammation (10). It is likely that the variable magnitudes of T2m signals and changes in muscle observed in the literature reflect both the heterogeneity of IBM and patients being scanned at different stages in their disease course.

This study had several limitations that must be acknowledged. Due to challenges posed by the COVID-19 pandemic, participant numbers were further reduced at subsequent visits. Only 10 participants in the placebo arm were compared with 8 in arimoclomol group. This small sample size may have limited the ability to detect a treatment effect, and to more precisely estimate associations between clinical and qMRI variables. The small sample size of this study warrants particular caution when interpreting associations between changes in clinical assessments and changes in qMRI. It is important for further studies in larger study cohorts to be performed, in order to determine if these longitudinal associations observed in this study can be recapitulated. With regards to the MRI methodology, we only used one cross-sectional slice of the thigh rather than multiple slices or volumetric assessment. Furthermore, we only investigated intramuscular changes within the thigh, not calves or other skeletal muscles. We did not compare T2m and FFa measures against those of healthy controls. Although a strict imaging protocol was followed, the scans were performed across two separate sites and two different scanners, which may add some variability. Given that this study was performed in the context of a clinical trial, there may be a placebo effect enhancing performance in clinical outcome measures at the follow up visits.

In conclusion, despite the limitations, this study does add more support for the use of qMRI as an outcome measure in future clinical trials for IBM. FFa behaved similarly to Dixon derived FF, indicating its potential as a surrogate marker for FF. Furthermore, increase in T2m appeared to have strong association with a decline in certain clinical assessments. Therefore, it would be of benefit to explore these T2 derived measures in more detail and within larger cohorts, including a comparison with healthy controls. If validated further, T2 sequences could potentially be used in isolation to quantify both fat and water content of muscle. The use of T2 sequences alone in the context of clinical trials could help reduce costs, shorten

scan time and improve patient compliance. In the future, trials utilising larger participant samples undergoing qMRI, would provide more evidence on the usefulness of qMRI measures in clinical trials. Finally, the use of automated segmentation of lower limb muscles may also improve the ease in which qMRI analysis can be performed on a larger scale, and our group has already investigated the use of automated techniques in other neuromuscular disorders, demonstrating a similar level of responsiveness to manual segmentation (31, 32).

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Competing interests

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