Efficacy and safety of intravenous and subcutaneous immunoglobulin therapy in idiopathic inflammatory myopathy: A systematic review and meta-analysis

(Article begins on next page)

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Title: Efficacy and Safety of Intravenous and Subcutaneous Immunoglobulin Therapy in Idiopathic Inflammatory Myopathy: a systematic review and meta-analysis

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Abbreviations:

CI: confidence interval; CTD: connective tissue disease; DLCO: diffusion capacity of corbon mono-oxide; DPLD: diffuse parenchymal lung disease; EU: European Union; EUSTAR: European League against Rheumatism Scleroderma trial and Research; FVC: forced vital capacity; ILD: interstitial lung disease; mRSS: modified Rodnan skin score; SSc: systemic sclerosis

Abstract:

Objective: To perform a systematic review and meta-analysis on the efficacy and safety of intravenous (IVIg) and subcutaneous (SCIg) immunoglobulin (Ig) therapy in the treatment of idiopathic inflammatory myopathy (IIM) and juvenile dermatomyositis (JDM).

Methods: PubMed, Embase and SCOPUS were searched to identify studies on Ig therapy in patients with IIM and/or JDM (2010-2020). Outcome measures were complete response (CR) or partial response (PR) in terms of muscle power and extramuscular disease activity measures on the International Myositis Assessment and Clinical Studies Group (IMACS) core set domains.

Results: Twenty-nine studies were included (n=576, 544 IIM, 32 JDM). Muscle power PR with pooled Ig therapy was 88.5% (95% confidence interval (CI): 80.6-93.5, n=499) and PR with SCIg treatment was 96.61% (95% CI: 87.43-99.15, n=59). Pooled PR with first-line use of IVIg was 77.07% (95% CI: 61.25-92.89, n=80). Overall, mean time to response was 2.9 months (95% CI: 1.9-4.1). Relapse was seen in 22.76% (95% CI: 14.9-33). Studies on cutaneous disease activity and dysphagia showed significant treatment responses. Glucocorticoid and immunosuppressant sparing effect was seen in 40.9% (95% CI: 20-61.7) and 42.2% (95% CI: 20.4-64.1) respectively. Ig therapy was generally safe with low risk of infection (1.37%, 95% CI: 0.1-2.6).

Conclusions: Add-on Ig therapy improves muscle strength in patients with refractory IIM, but evidence on Ig therapy in new-onset disease and extramuscular disease activity is uncertain.

Keywords: idiopathic inflammatory myopathy; immunoglobulin therapy; IVIg; SCIg

1. **Introduction:**

The idiopathic inflammatory myopathies (IIMs) are a group of diverse and systemic diseases characterized by chronic autoimmune skeletal muscle inflammation[1]. Treatable subtypes of IIM include (juvenile) dermatomyositis ((j)DM), antisynthetase syndrome (ASS), immune mediated necrotizing myopathy (IMNM) and overlap/non-specific myositis (OM/NSM), of which many patients might have formerly been classified as having polymyositis (PM). Corticosteroids have traditionally been used as the first-line agent along with other agents like methotrexate, cyclosporine, azathioprine, mycophenolate mofetil and rituximab [2,3]. Add-on IVIg has been shown to be effective and safe in steroid refractory DM in an RCT [4,5]. Observational studies in PM have shown a relatively good safety profile along with a steroid sparing effect [2]. A narrative review on IVIg in IIM in 2012 did not include a systematic quantitative analysis of data[2], and new data are available. In the last decade several important advances have taken place like extension of use of immunoglobulin therapy (Ig therapy) among patients with juvenile dermatomyositis (JDM)[6], use of IVIg as first line therapy in IIMs [1,6,7], and use of subcutaneous immunoglobulin preparations (SCIg) among patients with IIM [8]. Therefore, we conducted this systematic review and meta-analysis to summarize data on efficacy and safety of IVIg and SCIg in the treatment of IIMs and JDM.

2. **Materials and Methods:**

We conducted a systematic review and meta-analysis on the efficacy and safety of Ig therapy in IIM. It was registered in PROSPERO (CRD42021242839) and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) check list.

2.1.1 Literature search:

PubMed, Embase and SCOPUS were searched with the following keywords: ((intravenous immunoglobulin OR IVIg) OR (subcutaneous immunoglobulin OR SCIg) OR (immunoglobulin therapy) OR (immunoglobulin preparation)) AND ((idiopathic inflammatory myopathy) OR IIM OR myositis OR polymyositis OR dermatomyositis OR juvenile dermatomyositis OR (necrotizing myopathy OR IMNM OR immune mediated necrotizing myopathy)). The last date of the search was 31st July 2020. The first date of the search was 1st January 2010. We organized the selected titles and abstracts on Zotero and uploaded to Covidence (Covidence, Melbourne, VIC, Australia). Retrieved articles' references were scanned for further relevant publications. Abstracts were screened after removal of duplicates followed by removal of redundant articles. Full texts of the included articles were retrieved.

2.1.2 Eligibility criteria and outcome measures:

The inclusion criteria of this study were the following: 1) availability of relevant information on patients' characteristics, along with baseline information on muscle strength testing (Manual Muscle Testing-8 (MMT-8) or Medical Research Council (MRC)) [9,10] ; 2) availability of information on diagnosis and subtype of IIM (idiopathic inflammatory myopathies: dermatomyositis (DM), immune mediated necrotizing myopathy (IMNM), anti-synthetase syndrome (ASS), non-specific/overlap myositis (NS/OM); or the "polymyositis (PM)" based on predefined diagnostic criteria); [11,12]; 3) intervention: at least one (sub)group of patients was treated with Ig therapy (either IV or SC) with or without other concomitant immunosuppressive agents; 4) availability of information on outcome measures: follow up of muscle strength test outcomes with or without other extramuscular disease activity measures, as defined below.

Outcome measures were categorized into complete response (CR) or any response (PR=at least partial response) in terms of muscle power at the following time points: six months and/or at the end-of-follow up. Since the criteria used for outcome assessment varied among studies (Table 1), the methods of assessment were classified broadly into the following three classes: physician assessment, defined clinical criteria and guideline based improvement criteria [13]. Wherever CR and PR were defined in the defined clinical criteria or guideline-based assessment criteria, such identifications were kept in-toto. One such example of pre-defined criteria would be as follows: "…remission as clinical improvement, assessed by MRC scale, and reduction in CPK levels lasting for at least 12 months. Patients who achieved a significant improvement in muscle strength… for at least 6 months were defined as partial responders…"[7]. All such criteria were carefully scrutinised for eligibility and included only after consensus opinion of two reviewers (R.P.G and S.H.). They are written in detail in table 1. Those studies which used only physician assessment without any predefined criteria, if the terms CR or PR were used then such data was extracted as it is otherwise, any improvement, otherwise unspecified, is taken as PR.

Extramuscular disease activity measures and response were selected based on the domains of the International Myositis Assessment and Clinical Studies Group (IMACS) core set, i.e., constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, cardiovascular and others [9,14,15]. All adverse events were recorded.

The exclusion criteria were the following: 1) single case reports; 2) case series with fewer than three patients; 3) narrative reviews; 4) studies in which myositis–specific outcomes, either in terms of muscle strength or in terms of extramuscular core sets, were not reported; and 5) studies on patients with inclusion body myositis (IBM) or cancer-associated myositis.

Studies with mixed baseline populations (patients with DM/IMNM/ASS/PM and IBM admixed together), were only included if the baseline and outcome measures could be extracted for the DM/IMNM/ASS/PM group separately from the IBM group. We did not exclude studies with previous treatment with immunosuppressive agents and we did not impose any language restriction.

2. 1.3Study selection and data abstraction:

Two reviewers (R.P.G. and D.B.) independently searched the databases and selected studies. Disagreements during selection procedure were resolved by discussion among three reviewers (R.P.G., D.B. and S.H.). Screening was done independently along with assessment for inclusion in line with the laid down eligibility criteria. The full texts of the relevant articles were retrieved for comprehensive review and in cases of discrepancy or confusion the authors were contacted. Data extraction was done by two reviewers (R.P.G and S.H.) independently and crosschecked with each other. The two reviewers employed a predefined form for data extraction. We extracted the following data: authors; year of publication; study design [observational prospective, observational retrospective and randomized controlled trial (RCT)]; baseline characteristics of patients, including the number of patients that met the inclusion criteria, age, gender, duration of IIM, number of patients with each subgroup (DM/IMNM/ASS/PM), adult or mixed population or purely JDM population, immunosuppression or immunomodulatory treatments other than Ig previous to and/or concurrent with Ig treatment; route of administration of Ig preparation (IV or SC); dose, number of cycles and interval between cycles of Ig therapy; duration of follow up; baseline muscle strength (by either MMT-8 or MRC score); number of patients at baseline with disease activity in the IMACS extramuscular core set; outcome measures (vide supra) at 6th month and/or at the end of follow-up; presence or absence of a control group and the control drug (actual

drug or placebo). For both intervention and control groups we extracted: end-of-follow up CR and PR for muscle power; number of patients without steroids or second immunosuppressive agents at the end-of-follow up; and adverse events and infections associated with the Ig therapy. The following sub-analyses were done in terms of muscle strength: Ig preparation as first line treatment; Ig preparation as add-on treatment and studies which used guideline-based improvement criteria.

2.2 Quality assessment:

Quality assessment was done using the Cochrane Risk of Bias tool for RCTs and the Newcastle–Ottawa Scale for the cohort studies [16–19]. Two reviewers (D.B. and U.K.) did quality assessment independently and disagreements were resolved after discussion among three reviewers (D.B., U.K. and R.P.G.) [17,19]. The quality assessment results are presented in Supplementary Tables S1 and S2.

2.3 Statistical methods:

Data represented as mean and standard deviation (SD) was kept verbatim and data represented as median and range were transformed into estimated mean and confidence interval (CI) through Hozo's transform [20]. Heterogeneity was calculated with the I^2 statistic, which represents the percentage of total variation across studies [21]. We used a fixed-effect model if I^2 was zero and a random-effects model if $I^2>0$. Sensitivity analysis was performed by removing conference abstracts, retrospective studies and outliers for each individual result, as data allowed [22]. To assess publication bias, Funnel plots were obtained. Since the basic assumption of symmetry of funnel plot is to assume normality of sample means and independence of sample mean from sample variance, and majority of our outcomes are binary data, therefore, for analysis of publication bias,

log odds was taken as the outcome measure and Harbord's test was performed [23]. This is a score-based method employed to approximate the log Odds Ratio, obtained by modifying a version of the Egger's test for binary data [24]. To investigate heterogeneity in muscle strength response subgroup analyses was planned in sequential manner against the following categorical covariates after removal of outliers: mode of administration of Ig therapy (IV versus SC), followed by population of individual studies (JDM versus adult population) and finally with method of assessment of muscle strength response [22,25]. A p value ≤0.05 was taken as significant publication bias. All statistical computations were done using the software R ver 4.0.0 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

3. **Results:**

3.1 Search results and characteristics of included studies:

PRISMA flow diagram of the search strategy is shown in Fig. 1 [26]. Overall, 2782 studies were identified and 175 studies were left for full text review after screening of duplicate, overlap and irrelevant studies. Finally, 29 studies were included in this meta-analysis (n=576) [1,5–8,27–50].

Baseline patient demographics are detailed in Table 1. Six included studies were conference abstracts (n=144), of which one of them has been published as a full-text article by the time of writing this paper[51]. We carefully scrutinized the conference abstracts and ensured that redundant ones were excluded. The included studies were conducted in 12 countries (Italy, France, Japan, the USA, Germany, Austria, Peru, Hungary, Czech Republic, The Netherlands, Canada, Qatar, Israel, Australia, Greece, Russia and Brazil). Four studies were only on JDM [6,27,40,41], and others had mixed or purely adult populations. The mean age of adult patients was 53 years (95% CI 48.3-58) from 18 studies (n=368) [1,7,8,28,29,31–34,36–39,42,45–48]and that of patients

with JDM was 8.8 years (95% CI: 7.7-10); available from three studies (n=21) [6,27,41]. The mean duration of disease was 11.4 months (95% CI 8.3-14.4) from 13 studies (n=256) [1,7,8,27,29,32,33,39,41,42,45–47].

Mean number of cycles of IVIg given was five (95% CI: 3-7) available from seven studies (n=178) [7,28,31–33,40,46]. Dose was most often 2g/kg/month every four weeks but varied between 1-3 g/kg/month. Dose of SCIg varied from 0.1-0.2 g/kg/week. Mean duration of follow up was 21.2 months (95% CI: 10.2-32, available from 18 studies).

3.2 Muscle strength improvement with Ig treatment:

Pooled reported CR rate after treatment with Ig therapy (IVIg and SCIg combined) was 63.57% (95% CI: 47.42-77.16, I^2=52%, p=0.01, 14 studies, n=198, Fig 2) [7,8,27,29,30,32,33,35,36,40,41,46,47,49] and pooled PR rate was 88.52% (95% CI: 80.64-93.45, I^2=74%, p=0.26, 27 studies, n=499, Fig 3) [8,8,27–29,31–35,37–41]. Pooled PR rate of muscle power improvement among patients on SCIg was 96.61% (95% CI: 87.43-99.15, I^2=0%, p=1.0, 5 studies, n=59, annexure 1) [8,29,30,39,41].

Significant improvements in muscle power scores were also observed both in terms of MMT-8 (mean improvement 6.1, 95% CI: 4.01-8.2, I^2=23%, p=0.26, 6 studies, annexure 1) [1,30,39,43,46,49] and MRC score (mean improvement 0.78, 95% CI: 0.24-1.32, I^2=80%, p<0.01, 4 studies, annexure 1) [7,8,29,32].

Mean reduction in CPK from baseline to end of follow up was 1340.73 IU/L ((95% CI: 593.3-2088.16, I^2=93%, p<0.01, 7 studies, annexure 5) [1,7,8,29,30,38,46].

3.2.1.Use of Ig therapy as first line therapy:

Ig therapy was used as the first line therapy in three prospective studies (n=26) [1,6,38]. All of the studies used only IVIg. Among these, the study by Liu et al had missing data in four out of eight patients. For the purpose of this meta-analysis, the data was extracted from the remaining four patients with adequate follow up data. The indications for first line use of IVIg were as follows: patients with diabetes and statin induced IMNM who refused glucocorticoids, protocolised treatment of JDM from registry data and investigator initiated clinical trial to test effectiveness as first line therapy. Three other retrospective studies used IVIg as first line therapies in patients with IMNM (n=54) [45-47[46–48]]. In a random effects model pooled muscle power improvement at least PR rate was 77.07% (95% CI: 61.25-92.89, I^2=69, p=0.005, please mention number of studies here somewhere). Response was observed within the first six months of therapy in the prospective studies.

3.2.2 Use of IVIg as add-on therapy:

Seven studies used Ig therapy as add-on due to refractory or resistant proximal muscle weakness (n=65) [8,28,31,36,42,43,48]. In a random effects model pooled muscle power improvement PR rate was 88.48% (95% CI: 80.18-96.78, I^2=66.92, p=0.005).

3.2.3. Use of Ig therapy in studies with guideline-based improvement assessment:

Five studies used well-defined guideline-based improvement assessment of muscle strength (n=113) [1,5,6,30,46] In random effects model pooled muscle power improvement PR rate was 78.23% (95% CI: 50.42-92.7, I^2=30, p=0.22). Improvement in muscle strength (at least PR) within the first six-months of follow up was noted in 68.11% (95% CI: 53.09-83.14, I^2=50, p=0.11).

3.2.4 Muscle strength improvement with Ig therapy compared to controls:

Four studies compared at least PR rate in IVIg group compared to placebo or other drugs (n=91 in IVIg group and n=109 in control group) [5,6,31,32]. Pooled risk ratio (RR) for at least PR in favour of IVIg compared to controls was 1.64 (95% CI: 1.3-2.06, I^2=0, p=0.56, Fig 4) [5,6,31,32].

There were two RCTs which compared the efficacy of IVIg in terms of muscle power improvement compared to control drugs (one with various immunosuppressant as control and another with only placebo) [5,31,51]. Pooled RR for PR in favour of IVIg was 1.73 (95% CI: 1.3-2.3, I^2=0, p=0.71, annexure 1).

3.3 Improvement in extramuscular disease activity:

Extramuscular core set according to IMACS were not uniformly reported in all the studies. However, the following core sets were reported adequately so that data could be pooled for meta-analysis: cutaneous involvement both in adult DM and JDM, dysphagia and ILD in adult patients. These results are summarised in table 2.

3.4 Six-month efficacy, time to response and relapse:

Pooled six-month muscle power improvement PR rate was 78.27% (95% CI: 67.27-86.32, I^2=56%, p<0.01, 16 studies, n=321, annexure 1) [1,5,6,8,28,31–33,36,38,43,44,46–49]. Improvement in dysphagia by six months was observed in 92.16% (95% CI: 85.09-96.03, I^2=0%, p=1.0, 3 studies, n=102, annexure 3) [28,43,49]. No studies were available on SCIg preparations with six-month remission rates so pooled estimates were not obtained.

Mean time to response in terms of muscle power was 2.98 months (95% CI: 1.91-4.05, I^2=88%, p<0.01, 4 studies, n=78, Fig 5) [36,46,48,50]. Mean time to response in cutaneous disease was 1.79 months (95% CI: 1.52-2.07, I^2=0%, p=0.86, two studies, n=92, annexure 2) [45,50].

Relapse after achievement of muscular response was seen in 22.76% (95% CI: 14.96-33.04, I^2=35%, p=0.15, 8 studies, n=143, annexure 1) [1,7,27,30,33,45,46,48]].Mean time to relapse of myositis after achievement of response was 7.09 months (95% CI: 2.29-11.09, I^2=98%, p<0.01, 3 studies, n=25, annexure 1) [27,32,33].

3.5 Steroid and immunosuppressant sparing effect:

Eight studies reported use of previous immunosuppressant: methotrexate in 107 patients, azathioprine in 49 patients, hydroxychloroquine in 46 patients, mycophenolate in 21 patients, cyclosporine in 8 patients, cyclophosphamide in 7 patients, rituximab in 7 patients, tacrolimus in two patients and anti-tumor necrosis factor inhibitor in one patient [6,8,28,34,36,37,41,45]. Two studies reported that seven and two patients respectively were on immunosuppressant drugs without specifying which drugs [1,31]. Concomitant immunosuppressant use was reported in 10 studies: methotrexate in 86 patients, azathioprine in 36 patients, hydroxychloroquine in 27 patients, mycophenolate in 14 patients, cyclosporine in 4 patients, cyclophosphamide in 6 patients, rituximab in 6 patients and chloroquine in one patient [7,8,32–34,41,42,46–48]. Two studies did not use any other immunosuppressant agents [1,38].

Baseline prednisolone dose was 25.8 mg/day (95% CI: 18.8-32.8, I^2=97%, p<0.01, 7 studies, annexure 4) [7,8,29,31,34,43,49]. At the end of follow up prednisolone was reduced by a mean of 14.67 mg/day (95% CI: 7.81-21.54, I^2=95%, p<0.01, 5 studies, annexure 4) [7,29,34,43,49]. Prednisolone could be discontinued in 40.9% of patients (95% CI: 20-61.73, I^2=86%, p<0.01, 6 studies, annexure 4) [8,30,34,37,43,46,48]. Other immunosuppressant could be discontinued in 42.2% of patients (95% CI: 20.35-64.05, I^2=81%, p<0.01, 6 studies, annexure 4) [8,27,30,34,46,48].

3.7 Sensitivity analysis:

We performed a single-step sensitivity analysis of the above-described results after removing conference abstracts, retrospective studies and outliers. These results are summarized in Table S3 and in annexure 1-4.

3.8 Publication bias:

Publication bias was represented with funnel plots and Harbord's tests (Supplementary Table S4 and annexure 1-5). There was no significant publication bias as all P-values were >0.05.

3.9 Adverse events:

Fifteen studies including 330 patients reported on adverse events attributed to Ig preparations [1,7,27–29,32–35,39,41,42,45,46,49]. Of these, transient fever and infusion site reactions and headache were the commonest occurring in 25 patients each. Other reported adverse events were as follows: nausea in seven patients, hypertension in five patients, skin rashes in three patients, aseptic meningitis in two patients and one patient reported chest pain. Venous thrombosis and pulmonary embolism was reported in five (out of 101 patients, 4.32% (1.33-8.91), I^2=0, p=0.72) patients among which only study reported a possible precipitating factor (ovarian cancer, n=1) and the others did not report any risk factors.[1,29,42,45] Aspiration pneumonia occurred in six patients, but was in all likelihood related to myositis disease activity rather than treatment related adverse effect. Infections were particularly uncommon and occurred in 1.37% of patients (95% CI: 0.1-2.64, I^2=0%, p=0.97, 13 studies, n=306) [1,7,27–29,32–34,41,42,45,46,49]. All the patients who had an infectious adverse effect received either multiple concomitant immunosuppressants or previous immunosuppressants just prior to initiation of Ig therapy. However due to lack of data, no formal analysis could be done.

3.10 Subgroup analysis:

To account for the heterogeneity in muscle power CR and PR, subgroup analyses were done. In the first subgroup analysis, based on mode of administration of Ig therapy (IV, 87%, 95% CI: 82-92, n=403 versus SC, 97%, 95% CI: 93-100, n=59), there were significant subgroup differences between the two modes of administration in muscle power PR (Q=51, df=24, p=0.0008, annexure 6). There is no heterogeneity in the subgroup SCIg requiring further exploration. However, there is significant heterogeneity in the IVIg group. In the next step, in the IVIg group further subgroup analysis was done based on study population (JDM only versus adult only: JDM: 92%, 95% CI: 79-100, n=15 versus adult, 86%, 95% CI: 81-91, n=363). There were significant subgroup differences (Q=38.07, df=17, p=0.0024, annexure 6). In the JDM subgroup there is no further heterogeneity, but significant heterogeneity remained in the adult subgroup. Further subgroup analysis was done among the studies on adult population based on criteria used for assessment of improvement (physician assessment (87%, 95% CI: 81-94, n=248) versus predefined clinical criteria (94%, 95% CI: 87-100, n=37) versus guideline-based improvement assessment (75%, 95% CI: 67-84, n=78)). There were significant subgroup differences(Q=37.5, df=15, p=0.001, annexure 6). There was no heterogeneity in the groups assessed by predefined clinical criteria or guideline-based improvement criteria but significant heterogeneity still persisted in the subgroup assessed by physician assessment.

4. Discussion:

The idiopathic inflammatory myositis (IIM) are a group of chronic immune mediated disorders that mainly affect the skeletal muscle along with diverse clinical manifestations like dysphagia and respiratory muscle involvement, cutaneous affections which especially in children are often

marked and resistant to treatment and interstitial lung disease among others [8,39]. Treatment is a challenge and is based on the backbone of glucocorticoid [[8]. Despite availability of various agents like methotrexate, azathioprine, cyclosporine, tacrolimus or rituximab only a minority achieve a durable remission and even then it may take as long as 60 weeks on an average. With these treatments adverse effects like infections are also common [39].

Our meta-analysis demonstrated at least partial efficacy with improvement of muscle weakness in 89% of patients with refractory IIM, and indicated at least partial efficacy on improving muscle weakness as first-line therapy in 77% of patients with newly diagnosed IIM. The improvement was commensurate with significant reduction of CPK from baseline (mean fall 1340.73 IU/L) and improvement in global clinical indices of muscle power improvement like MMT-8 or the MRC. Mean time to achieve these responses was approximately 3 months. Improvement in muscle power allowed reduction in prednisolone doses by an average of almost 15-mg/day and prednisolone could be discontinued in 40.9% of patients and other immunosuppressant could be discontinued in 42.2% of patients. A previous systematic review [50[52]], on immunosuppressive or immunomodulatory therapy in IIM, included one placebo-controlled trial on IVIg [51[4]], on eight patients with treatment resistant dermatomyositis, noted that Ig therapy improved muscle scores significantly over three months. This rapid response in terms of muscle power with Ig therapy is of particular importance, as IIMs tend to improve very slowly over months with conventional therapy. Even in the RIM trial on rituximab which showed a high clinical response of 83%, the median time to achieve a clinically meaningful response in muscle power was just over 20 weeks [3[3]]. However, presence of heterogeneity and absence of head-to-head studies makes it difficult to draw a conclusive statement. Two RCTs were included in our analysis, which compared IVIg to placebo in one and various immunosuppressants in the other. The pooled result was devoid of

heterogeneity and favoured IVIg over controls (RR: 1.73, 95% CI: 1.3-2.3). However, this is an early result and should be interpreted with caution.

There are two further points regarding muscle power improvement, which merit discussion. It is apparent from the present analysis that the above-mentioned benefit may be extended to SCIg as well. We observed that muscle power improvement is documented in 96.61% (95% CI: 87.43-99.15) of subjects with SCIg preparations. Subgroup analysis did not reveal any significant heterogeneity in the results. But the number of subjects examined was small and needs larger studies for confirmation. There have been suggestions that even if SCIg acts in a similar way as IVIg does its mode of action still remain speculative, and it is conceivable that IVIg and SCIg acts at different stages in IIM disease activity. The high-dose administration via the intravenous route of Ig therapy (about 2 g/kg/monthly) leads to higher serum IgG peaks, which may account for the rapid onset of action. The subcutaneous route with low/medium dosage of Ig (<1-g/kg/monthly) is aimed at a steady-state serum IgG level that probably influences mechanism(s) of IIM related damage, such as regulation of activity of T cells and dendritic cells. Therefore, while the onset of action may be delayed compared to IV route of administration the effects may be more sustained [29].

The second important result of the present analysis is the utility of Ig therapy as a first line therapy in IIM. Cherin et al published one of the earliest studies on Ig therapy in IIM as the first therapy and showed modest improvement in three out of 11 patients and biochemical improvement in eight patients[53]. In recent years however there have been three prospective studies evaluating the effectiveness of Ig therapy as a first line therapy in IIM [1,6,38]. These included one observational prospective cohort study on IVIg monotherapy as first-line therapy in newly diagnosed IIM, one observational prospective cohort study on IVIg as add-on therapy in a multimodal first-line therapy

in JDM and an observational study on IVIg monotherapy as first-line therapy in newly diagnosed statin-associated IMNM. The other three retrospective studies included in the pooled results, which used IVIg as first line therapy, all treated patients with IMNM. Pooled results indicated an improvement (at least minimal) in around 77% of patients. However, the included number of patients was small (n=80) and at least one study had significant missing data. In one study, the onset of improvement was within 3 weeks[1] while this is estimated to be between 4-12 weeks with high dosed glucocorticoid therapies [54].

The side effects associated with IVIg are relatively fewer as compared to other conventional therapies like steroids, azathioprine and methotrexate, especially infections. In the present study infections as a side effect of IVIg were particularly uncommon and occurred in 1.37% of patients. Other reported life-threatening complications of IVIg, like thromboembolism, occurred with slightly higher frequency (~1.5%).

Since the first report of its use in PM by Roifman et al. in 1987,[52]and later by Dalakas et al in 1993,[4] clinical studies have shown efficacy of IVIg for the treatment of IIM especially in adult patients [31]. Since the first systematic review undertaken by Wang et al more than a decade ago, [2] several new studies have come up, results of which we have summarized above. The therapeutic benefits of Ig therapy could be linked to their anti-inflammatory and immunomodulatory properties like anti-idiotype antibodies, cytokine and complement regulation, antibody-dependent cytotoxicity (ADCC), and cell-cell interaction inhibition [55]. IVIg has also been shown to increase the intracellular expression of transforming growth factor (TGF-β) and enhance the suppressive effect of CD4+CD25+ regulatory T cells in in-vitro studies.[56]

Clinically speaking the use of Ig therapy may be preferred to the use of high-dose glucocorticoids

and/or immunosuppressants in several conditions: cancer-associated myositis, IIM associated with chronic infections or immunodeficiency, pregnancy or the planning of a pregnancy, conditions with contraindications to prolonged glucocorticoid treatment like diabetes. Use of IVIg as an immunomodulatory compound has been explored with success in patients with other rheumatic diseases like lupus and several other autoimmune conditions such as immune thrombocytopenic purpura (ITP), macrophage activation syndrome, vasculitis (polyarteritis nodosa) and non-rheumatic diseases like optic neuritis, acute inflammatory demyelinating polyradiculopathy [57–59]. Use of IVIg in several autoimmune diseases like ITP, lupus, myasthenia gravis, pemphigus vulgaris and IIM, has been associated with a corticosteroid sparing effect.[60] Indications of SCIg over IVIg are difficult venous access, past thromboembolic events, IgA deficiency, renal impairment, and cardiac involvement due to myositis [29,30]. SCIg can also be used as a rescue therapy for patients who had a previous reaction to IVIg.

The limitations of the study are several. Lack of uniformity in terms of definitions of improvement is a major limitation. However, this limitation is inherent in meta-research and the subgroup analysis addressed this limitation to some extent. Significant heterogeneity in terms of different types of articles included in the study, inclusion of conference abstracts and lack of uniformity in the included control groups are the other limitations. Another area in which data were sparse and could not be explored systematically was the extramuscular features of IIM among which only dysphagia and cutaneous disease has been studied substantially and ILD has been studied relatively less frequently.

Nevertheless, this is, to the best of our knowledge, the first aim to quantitatively analyse this topic. We included only recent studies published over the past decade. The use of Ig therapy has been conventionally reserved for resistant or relapsed disease and life-threatening complications.

Relatively new information which our analysis affirms are, improvement in muscle strength in more than three quarters of patients when used as a first line therapy and this response appears within the first three months with a commensurate steroid sparing effect both with IVIg and SCIg; and additional efficacy of Ig therapy in resistant cutaneous disease, life threatening dysphagia, utility in JDM and possible effectiveness in stabilizing ILD.

Conclusion

Both IVIg and SCIg led to improvement of muscle power, skin rash, and dysphagia in most patients in both newly diagnosed and refractory myositis. However, the quality of included studies was generally low. The effect of Ig therapy was relatively rapid, with improvement in disease activity within three months. Ig therapy had a significant steroid sparing effect and it was possible to withdraw other immunosuppressant in almost half of the patients. In this study Ig therapy had a very good safety profile. Use as first-line therapy and SCIg should be examined in future studies.

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(IBMFRS), Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), Cutaneous Assessment Tool (CAT), Dermatomyositis Skin Severity Index (DSSI), Skindex, and Dermatology Life Quality Index (DLQI). Arthritis Care Res 2011;63 Suppl 11:S118-157. https://doi.org/10.1002/acr.20532.

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Figure Legends:

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of study selection process for this systematic review and meta- analysis.

Figure 2: Forest plot of complete remission of muscle power

Figure 3: Forest plot of at least partial remission of muscle power

Figure 4: Forest plot of at least partial remission of muscle power after excluding outlier between IVIg group and control group.

Figure 5: Forest plot of time to remission in achieving at least partial remission in muscle power

Supplementary figure legends:

ANNEXURE 1

Figure S1: Forest plot of at least partial remission of muscle power in the SCIg subgroup

Figure S2: Forest plot of manual muscle testing-8 (MMT-8) score before and after therapy with immunoglobulin preparation

Figure S3: Forest plot of medical research council (MRC) score before and after therapy with immunoglobulin preparation

Figure S5: Forest plot of at least partial remission of muscle power including only randomised controlled trials

Figure S13: Forest plot of at least partial remission of muscle power within first six months

Figure S16: Forest plot of proportion of relapse after achieving response (outliers excluded)

Figure S17: Forest plot of time to relapse after achieving response

Figure S22: Forest plot of complete remission of muscle power (senstivity)

Figure S23: Forest plot of at least partial remission of muscle power (sensitivity)

Figure S28: Forest plot of at least partial remission of muscle power within first six months (sensitivity)

Figure S30: Forest plot of manual muscle testing-8 (MMT-8) score before and after therapy with immunoglobulin preparation (sensitivity)

ANNEXURE 2

Figure S6: Forest plot of complete remission of cutaneous disease

Figure S7: Forest plot of at least partial remission of cutaneous disease

Figure S8: Forest plot of at least partial remission of cutaneous disease in patients with juvenile dermatomyositis

Figure S9: Forest plot of pre and post treatment CDASI

Figure S15: Forest plot of time to achieve a response in cutaneous disease

Figure S24: Forest plot of complete remission of cutaneous disease (sensitivity)

Figure S25: Forest plot of at least partial remission of cutaneous disease (sensitivity)

Figure S40: Funnel plot of complete remission of cutaneous disease

Figure S41: Funnel plot of at least partial remission of cutaneous disease

Figure S42: Funnel plot of at least partial remission of cutaneous disease (sensitivity)

ANNEXURE 3

Figure S10: Forest plot of complete remission of dysphagia

Figure S11: Forest plot of at least partial remission of dysphagia

Figure S12: Forest plot of proportion of patients with stability in symptoms of interstitial lung disease

Figure S14: Forest plot of at least partial remission of dysphagia within first six months

Figure S26: Forest plot of complete remission of dysphagia (sensitivity)

Figure S27: Forest plot of at least partial remission of dysphagia (sensitivity)

Figure S43: Funnel plot of complete remission of dysphagia

Figure S44: Funnel plot of complete remission of dysphagia (sensitivity)

Figure S45: Funnel plot of at least partial remission of dysphagia

Figure S46: Funnel plot of at least partial remission of dysphagia (sensitivity)

Figure S47: Funnel plot of at least partial remission of dysphagia within first six months

ANNEXURE 4

Figure S18: Forest plot of baseline dose of prednisolone in mg/day

Figure S19: Forest plot of prednisolone dose before and after therapy with immunoglobulin preparation

Figure S20: Forest plot of proportion of patients discontinuing prednsiolone at the end of follow up

Figure S21: Forest plot of proportion of patients discontinuing other immunosuppression agents at the end of follow up

Figure S32: Forest plot of prednisolone dose before and after therapy with immunoglobulin preparation (sensitivity)

Figure S50: Funnel plot of reduction in daily prednisolone dose

ANNEXURE 5

Figure S4: Forest plot of creatine phosphokinase before and after therapy with immunoglobulin preparation

Figure S29: Forest plot of creatine phosphokinase before and after therapy with immunoglobulin preparation (sensitivity)

Figure S54: Funnel plot of creatine phosphokinase before and after therapy with immunoglobulin preparation

Figure S55: Funnel plot of creatine phosphokinase before and after therapy with immunoglobulin preparation (sensitivity)

ANNEXURE 6

Figure S56: Forest plot of subgroup analysis (step 1: IV (subgroup 1) versus SC (subgroup 2))

Figure S57: Forest plot of subgroup analysis (step 2: JDM (subgroup 1) versus adult (subgroup 2))

Figure S58: Forest plot of subgroup analysis (step 3: physician assessment (subgroup 1) versus predefined clinical criteria (subgroup 2) versus guideline informed criteria (subgroup 3))