A systematic review on biological therapies in juvenile idiopathic inflammatory myopathies: an evidence gap in precision medicine

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Abstract

Objective

Juvenile idiopathic inflammatory myopathies (JIIMs) are a heterogeneous group of systemic autoimmune diseases. Juvenile dermatomyositis (JDM) is the predominant form of JIIMs, and is a rare, chronic autoimmune illness characterised by symmetric, proximal muscle damages and involvement of the skin. In the last two decades, the use of monoclonal antibodies has also been expanded to JIIMs; however, there is limited evidence on use of these treatments. We assessed the efficacy/effectiveness and safety of biologic agents in JIIMs.

Methods

A systematic literature review was conducted using Embase®, MEDLINE®, MEDLINE®-In Process and Cochrane library to identify studies on biologics agents in JIIMs published in English language as full-text articles (1975 to December 2020) or conference abstracts (2000 to December 2020).

Databases were searched with the key words regarding chronic myositis crossed with "biologic agents OR tocilizumab OR rituximab OR adalimumab OR infliximab OR anti-TNF OR etanercept". Of note, we did not include children, age, or age limits in the search as medical subject headings terms because we may have been able to extract a sub cohort of children from studies including both children and adults.

Results

Of the 1633 retrieved publications, 18 articles were identified for a total of 165 patients. In real-world studies, definition of complete (CR) or partial response (PR) varied. JIIMs patients were most often treated with anti-TNF (88 pts); patients received etanercept (ETA), 48 patients infliximab (IFX), 4 patients received adalimumab (ADA). In other 15 patients IFX was followed by ADA. Rituximab (RTX) was used in 73 children. A single case series reported the use of abatacept (ABA) in 4 patients. Despite the reduced number of treated patients, complete response on myositis was reported in 29.6% (8/26) patients treated with at least one anti-TNF and in 38% (10/26) treated by RTX. Complete response of skin vasculitis has been reached in 33% (4/12) children on anti-TNF and in 36% on RTX (21/58). Anti-TNF agents might be efficient in treating calcinosis lesions.

Conclusion

Currently, the available evidence regarding the use of biologic treatment in JIIMs results quite limited but suggest a promising the use of anti-TNF agents and RTX in treating active JIIMs. Anti-TNF treatment might have a role in treating calcinosis. However, an overall very low quality of the available studies and multiple confounding factors hamper to suggest a treatment over another. Thus, randomised clinical trials are urgently required to attempt the optimal treatment in real-world setting.

Key words

juvenile idiopathic inflammatory myopathies, juvenile dermatomyositis, inflammatory myopathies, biologic agents, rituximab, infliximab, anti-TNF, etanercept, abatacept, efficacy, safety

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Introduction

Juvenile idiopathic inflammatory myopathies (JIIMs) are a heterogeneous group of childhood-onset systemic, autoimmune diseases. Juvenile dermatomyositis (JDM), the predominant form occurring in children, represents the 85% of cases (1-3). In this condition, a systemic vasculopathy resulted in damage inside muscle, skin and organs, leading to the characteristic muscular weakness, increased muscle enzymes and pathognomonic skin rashes (4). Besides the typical skin and muscle involvement, other vital organs (*i.e.* lung, heart, gastrointestinal system) might be affected by the inflammatory process, exposing the child to life-threating complications (4).

Polymyositis accounts for 4–8% of all myositis cases, whereas myositis overlapping with other connective tissue diseases constitutes 6–12% of JIIMs (1-3).

The phenotypic variability of JIIMS might result in different organ involvement, variable disease trajectory and overall-prognosis. Despite a highly heterogeneous spectrum of the disease, several studies have led to the identification of specific subset characterised by specific clinical features. In particular, autoantibodies have shown to identify patient phenotypes, as in each patient usually only one type of the so-called myositis-specific autoantibodies (MSAs) or myositis-associated autoantibodies (MAAs) is found (5).

The identification of MSA or MAA has also a prognostic value, as several MSA have been shown to be associated to a worse prognosis in JIIMs. For example, anti- transcriptional intermediary factor 1 gamma (TIF-1γ) have been associated to a more severe skin involvement, with frequent lipodystrophy or skin ulceration (6).

The presence of anti-NXP2 antibody is associated with histological features of severe muscle ischaemia, thus leading to profound muscular weakness, and high risk of gastrointestinal perforation, due to a severe vasculopathy. This JIIM phenotype often requires multiple immunosuppressive treatments (7).

Anti-signal recognition particle (SRP) and anti-hydroxy-metylglutaryl coenzyme A reductases (HMGCO) antibodies features a different phenotype characterised by severe necrotising myositis, with scant inflammatory infiltrates and mild or absent skin involvement, and a severe disease course with need of multiple immunosuppressive treatment (8).

The JIIM treatment are borrowed from studies performed in JDM patients, without any attempt to stratify patients according to clinical characteristic or MSA profile (5).

Disease-modifying anti-rheumatic drugs (DMARDs), such as Methotrexate or cyclosporin, in addition to glucocorticoids represents the current mainstanding therapeutic approach (9).

However, 30% of treated children with JDM shows a resistant course (10) and, in real-world setting, several other treatments (IVIG, intravenous cyclophosphamide, plasma-exchange) have been attempted as second-line strategies for unresponsive patients. Available evidence suggests a worse prognosis for the other JIIMS (8, 11).

Due to the lack of randomised trials, these therapies have not been standardised yet, thus leading to a wide off-label use.

In the last two decades, the use of monoclonal antibodies has also been expanded to JIIMs, with a preference for B-cell depleting or anti-TNFα agents. As these medications might indeed represent a promising and safe therapeutic option, assessing the current evidence about their use in JIMMs became a mandatory need.

To date, no systematic evaluation on biologic treatment has been provided in JIIMs. The aim of our study is to examine the efficacy and safety of the currently used biologic agents for treating JIIMs.

Material and methods

We retrieved current evidence on the efficacy and safety of Biologic agents for JIIM treatment by a systematic literature review. The results are shown according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews (12).

Eligibility criteria

To include eligible studies, patients were required 1) to have disease onset

at or before the age of 16 years; 2) to start treatment before the age of 18; 3) to have JIIMs with persistent muscular inflammation and/or skin involvement and treating physician decided to start any biologic treatment 4) to be naive to any biologic treatment and 5) to be starting one of the available biologic treatments for children as the first biologic response modifier immunosuppressant medication. Furthermore, to be eligible, studies were required 1) to include standardised outcome measures assessing the effectiveness of treatment; in case of lack of definition of the response according to a standardised tool, improvement according to the physician judgement was accepted, if clearly stated; 2) to include at least 6-month period of follow-up. The International Myositis Assessment and Clinical Studies Group (IMACS) define complete clinical response as a 6-month continuous period of no evidence of disease activity while still on myositis therapy (13). In order to assess the effectiveness of treatment, we judged inactive disease using this criterion.

The exclusion criteria were: 1) starting time of biologic administration after 18 years of age, 2) lack of outcome measurement in JIIMs activity, 3) studies not reporting biologic treatment administered as the first biologic treatment; and 4) individual case reports, because their publication was likely importantly related to a positive outcome. We considered case series, retrospective studies, and open label studies. Case series were subdivided into moderate/large if they had 4 or more cases or small if they had less than 4 subjects.

Outcome measures

To assess efficacy in both the domains, we separately analysed muscle and skin involvement, as residual rashes frequently remain after muscle remission is reached. The main outcome measure used to assess the biologic treatment efficacy on muscle involvement was a ≥6-month continuous period with no evidence of disease activity while still receiving myositis therapy, according to IMACS definition of complete clinical response. When not clearly stated, data on muscle strength, Childhood Myositis Assessment Scale (CMAS) score, enzyme levels, magnetic resonance imaging findings were extracted from each study to define complete clinical response.

When available, we also extracted data on remission, according to the IMACS definition of a 6-month continuous period of no evidence of disease activity while off myositis therapy. For skin disease, complete response was defined as clearance of cutaneous rashes.

Efficacy of biologics on calcinosis was defined as absence of new lesions and no further expansion of the existing ones.

We defined partial response every improvement in each domain, not fulfilling the definitions of response reported above. Lack of improvement and the need to switch to other treatment was considered as a failure.

Information source

Publications included in the present review were retrieved using a computerised search of the following databases: EMBase, Ovid Medline; Evidence- Based Medicine (EBM) Reviews: American College of Physicians Journal Club; EBM Reviews: Cochrane Central Register of Controlled Trials; EBM Reviews: Cochrane Database of Systematic Reviews, and EBM Reviews: Database of Abstracts of Reviews of Effects.

Publications, as full-text articles, between January 1975 and February 2020, and conference abstracts between January 2000 and December 2020 were included.

Search strategy

Databases were searched with the key words "chronic myositis", or "dermatomyositis", or "inflammatory myopathies", or "refractory myopathies", or "refractory myositis", or "autoimmune myositis", or "inflamma$ myo$" crossed with "biologic agents" OR "tocilizumab" OR "rituximab" OR "adalimumab" or "infliximab" or "anti TNF" or "etanercept" or "abatacept". Of note, we did not include children, age, or age limits in the search as medical subject headings terms because we may have been able to extract a subcohort of children from studies including both children and adults. No limitation regarding the type of the study was entered. This strategy excluded records related to infectious and/or metabolic myopathies/myositis.

Study selection

Two reviewers (SAR, EM) independently screened the retrieved titles and abstracts and excluded duplicates and those obviously irrelevant. If the information in the abstracts was insufficient to make a decision, full papers were retrieved. Full papers of the selected articles were examined to determine whether they satisfied the criteria (SAR, VM, IM) and then confirmed by a second reviewer (EM). The references of all eligible articles including reviews, expert opinion papers and systematic reviews were manually searched for potentially eligible publications. During consensus meetings (SAR, EM, VM, IM, GS), disagreements of selections were resolved. In addition, we contacted authors of studies to determine whether data on an eligible subgroup were available.

Data extraction and items

Data were extracted, independently, by two reviewers (SAR, EM) using a standard form, and checked by a third reviewer (GS). The data items extracted were as follows: study design, study start/end dates, length of follow-up, aim of the study, characteristics of participants (number of children, gender, age and associated conditions), previous and concomitant treatment, type of biological drugs and the administered dose, outcome measures and adverse effects.

Results

Adhering to PRISMA guidelines, of the 1633 retrieved publications, 1417 papers were excluded by examination of their titles and abstracts (Fig. 1).

Excluded studies were mainly investigations that did not report paediatric cases, duplicates, review, studies that do not address biologic therapy in paediatric cases.

The full text of the remaining 216 studies was scrutinised. From the selection

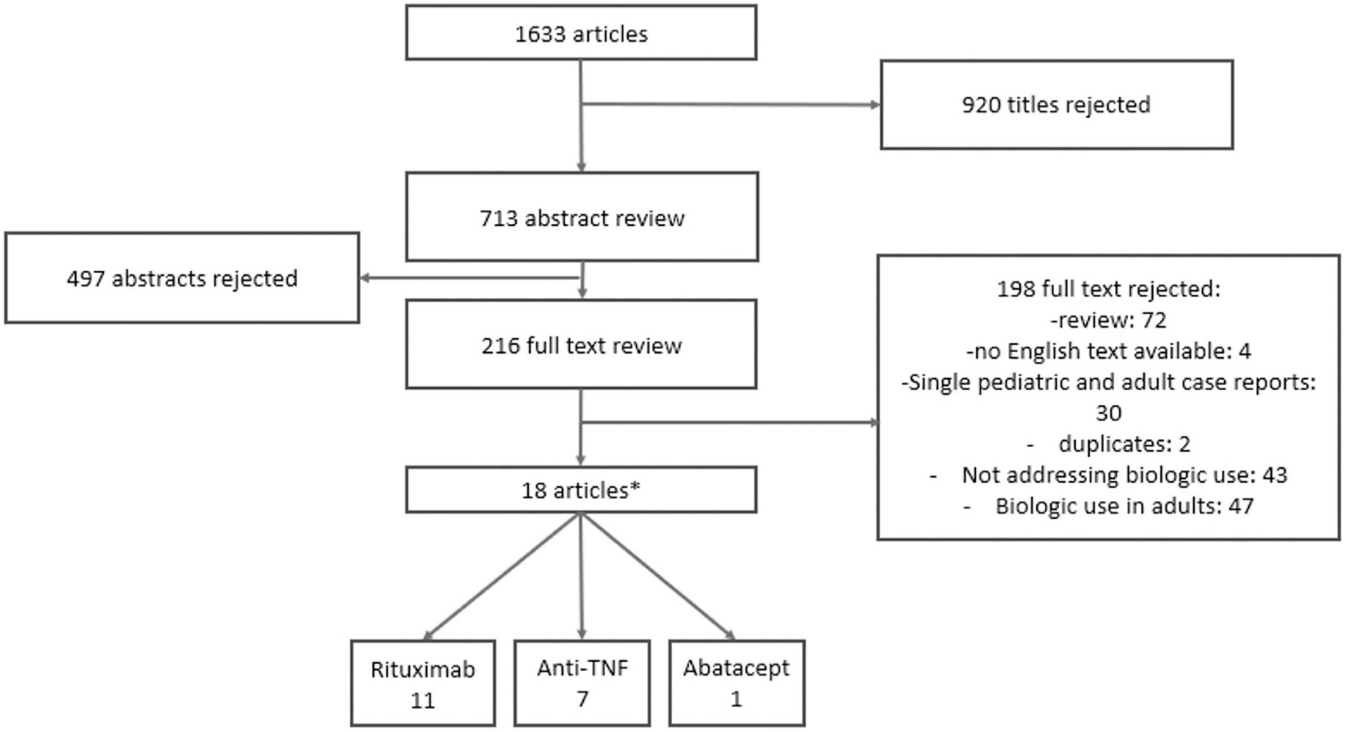

Fig. 1. Diagram of the identification literature research.
*A single study included patients treated either with anti-TNF or rituximab.

process, a total of 18 relevant articles were deemed eligible: 11 on RTX (14-24), 7 on Anti-TNF-α agents (24-30), 1 on Abatacept (31). The article from Tansley *et al*. included patients treated with either infliximab (IFX) or RTX (24). Of these 18 articles: 5 are case reports and small case series with at least 1 paediatric patient (3 related to RTX, 1 to anti-TNF; 1 both RTX and anti-TNF), 11 are case series (5 regarding RTX and 5 regarding anti-TNF, 1 abatacept) and 2 are a sub-analysis of randomised controlled trial for RTX. A total of 165 patients received biologics agents. Clinical features are summarised in Table I. Female sex was reported for 115 patients (71%); no data were available for 4 patients. Presence of myositis-specific antibodies were reported for 76 patients; anti-TIF1γ were detected in 32 patients, anti-NXP2 in 23 patients, anti-MI2 in 7 patients, anti-MDA5 in a single patient, anti-PL-7 in a single patient, anti-synthetase not otherwise specified in another patient. Seven other patients presented an anti-SRP positive JIIM and 4 with HMGCR-JIIM. Median age at treatment with biologic agents was 15.3 years (range 7.4–18; data were not available for 75 patients) and median length of disease was 38 months (1 month (14)-129 months (27); data were not available for 11 patients).

According received treatment, the 165 patients have been divided in three groups: a group treated with RTX (n=73), one with anti-TNF (n=88) and an additional one, treated with different biological drugs (n=4). Response to skin and muscle disease was separately assessed and the results are summarised in Table II and III, respectively.

Rituximab

The only one identified RCT was the Rituximab in Myositis (RIM) trial (32): in the RIM trial no paediatric data regarding efficacy on myositis could be extracted since they were reported as aggregate. The study from Rider *et al*. was an analysis of a subgroup of patients belonging to the RIM trial; thus, paediatric data on efficacy on active myositis could be extrapolated for 4 patients (19). On the contrary, a *post-hoc* analysis from the RIM trial data has been published from the same authors to investigate efficacy of RTX on skin disorders in 48 JDM patients (22).

Including the other 9 studies, RTX administration was reported in 73 cases (51 females, 22 males). 68 patients were affected by JDM, 5 patients suffered from other JIIM (3 anti-SRP myositis (20); 2 anti-HMGC myositis (24)). Median age was 15.3 years (range 5.3–16 years). 4 patients from the Agarwal study did not complete the follow-up. Disease length was 6.8 years (range 1 month-8.4 years) (18).

Eighteen patients received 375 mg/m^2 body surface area, administered as an IV infusion once a week for 4 weeks. The 48 patients extrapolated from the RIM trial received 575mg/m^2 at each infusion if body square area was ≤1.5 m2, and adults and children with a BSA >1.5 m^2 received 750 mg/m^2 up to 1 gram/infusion. In the study from Rider *et al*. one patient in the 'rituximab early' arm received drug at weeks 0 and 1 and placebo infusions were given at weeks 8 and 9. Conversely, 3 subjects in the 'rituximab late' arm received placebo infusions at weeks 0 and 1 and rituximab at weeks 8 and 9 (19).

In 9 studies efficacies of RTX on muscle involvement was assessed; 3 studies also analysed the efficacy on skin disease while two studies evaluated only the efficacy of RTX on skin manifestations.

When analysing efficacy for myositis (n=26), complete response was reported for 10 children treated with RTX. Due to severe capillary leak syndrome, in one patient RTX was combined with plasma exchange. Partial response was seen in 9 other patients. Lack of efficacy was reported for the other 7 patients. Two patients in the study of Bader-Meunier *et al*. were excluded by the analysis as data on the outcome after treatment with RTX were not available (18). In the study from Tansley *et al*. a patient unresponsive to RTX, was successfully treated later with IFX.

Fifty-eight patients were evaluated for efficacy on skin vasculitis; efficacy on calcinosis was evaluated in 32 patients. RTX induced at least a partial improvement in skin rashes in 50 out of 58 treated children, with 21 patients showing complete response. In the study from Agarwal *et al*. RTX was efficacious on several skin manifestations: cutaneous ulcerations (8/10 responsive patients), erythroderma (14/19), erythematous rash without ulceration or necrosis (35/40), heliotrope (28/33), Gottron sign/papules (21/44), periungual capillary changes (14/37) and focal alopecia (5/5). At the last follow-up, fifteen patients had resolution of any dermatomyositis rash.

Other skin manifestation were only poorly responsive to RTX: panniculitis (2/5), erythematous rash with secondary changes of ulceration or necrosis (5/15), diffuse alopecia (4/12) or mechanic hands (3/5) (22).

On the contrary, RTX was not effective in treating calcinosis: only 1 patient experienced complete response, 3 partial responses and lack of efficacy in the remaining other 28 patients as reported in Table III.

In the same cohort, three patients had gastrointestinal involvement: RTX was effective in two patients with active inflammation, whilst RTX did not confer any benefit in another one with diffuse gastrointestinal lipomatosis.

Mean follow-up duration was 17.2 months (median 11 months, range 10.5-50 (14, 20)). One patient from Cooper *et al*. experienced two relapses during the follow-up time and required two additional RTX infusion at 12 months and 14 months; one other patient experienced a relapse 12 months thereafter (14). Dinh *et al*. reported a skin flare 9 months after the first cycle with need of retreatment and subsequent infusions every 4 months (21). On the contrary, in the French cohort the reconstitution of the B cell pool did not correlate with relapse in muscle inflammation (18).

Complete clinical remission was reached during the follow-up only from 3 patients, suggesting the severity of the disease in these cohort of patients.

Furthermore, three patients unresponsive to RTX were subsequently treated with autologous stem-cells transplantation due to severe disease (16, 17).

Regarding safety of the RTX, a total of 13 adverse events were reported: 9 infections; 3 infusion-related adverse reactions; 1 gastrointestinal perforation. In the study from Bader-Meunier *et al*., one patient experienced an acute related infusion reaction at the onset of the first infusion of RTX leaded to discontinuation of treatment (18).

Anti-TNFs

Considering all the eligible studies, anti-TNF was the most used biologic agent (53%). The majority of the extractable data have been obtained from a large retrospective study from Campanilho-Marquez *et al*. (30). A total of 88 patients received these medications; 61 were females and 27 males. Four patients were affected by anti-SRP JIIM, other 2 patients by anti-HMGCR JIIM. Median age was 12.1 years (6.25-18 years; data not available from 72 subjects), mean disease length was 3.1 years (1.1 -10.8, data not available from 5 subjects). Regarding specific anti-TNF-α agents, 19 patients received etanercept (ETA), 48 patients infliximab (IFX), 4 patients received adalimumab (ADA). In other 15 patients IFX was followed by ADA; 10 patients switched due to treatment inefficacy, 4 patients due to severe adverse events related to hypersensitivity reaction to IFX and 1 single patient switched because of preferred subcutaneous administration of the anti-TNF agent. Two patients were excluded from the study of Campanilho-Marquez due to infusion reaction after the first administration of the medication.

Four patients were treated with ETA, 8 of them received one dose of 0.4 mg/kg 2 time to week; the dosage was not specified in the other 11 patients. Sixty-three children were treated with IFX, in 54 of these 6 mg/kg every 4 weeks was used; 5 patients received a dose of 3 mg/kg (week 0-2-6, subsequently every 8 weeks), 3 patients received a dose variable between 3 and 4 mg/kg. For the other patient no information regarding IFX dose were available.

When analysing efficacy for active myositis (n=27), complete response was reported for 8 children treated with anti-TNF. In the retrospective study by Sun *et al*. a patient treated with ETN experienced disease relapse while under medication and required oral corticosteroids to reach inactive disease (29).

One patient in the study by Green *et al*. was excluded by the analysis due to transfer of care, and lack of results regarding efficacy of medication (28). Partial response was seen in 9 patients. In the study by Riley *et al*. one patient showed a marked increase of CMAS, reaching a score of 28/52 from a score before IFX administration of 3/52. Lack of efficacy was reported for the other 10 patients; 3 patients with anti-SRP JIIMS showed no response to IFX (25) while in other 7 children ETA was not efficacious in controlling disease (27-29). In the study by Rouster-Stevens *et al*. two patients with anti-SRP antibodies had a concomitant interstitial lung disease, in one of these ILD was unresponsive to IFX treatment (25).

From only three studies data on efficacy of anti-TNF on skin disease were extracted (n=12). In two studies anti-TNF induced at least a partial improvement in skin vasculitis in 10 treated children, with 4 patients experiencing complete response. Only two patients showed no response to anti-TNF-α (26, 27).

When assessing efficacy on calcinosis (n=25), 18 patients showed at least a partial response, with 8 patients experiencing complete clearance of the calcinotic lesions in the study by Campanilho-Marques *et al*. (30).

According to available data, no patients reached complete clinical remission after treatment with anti-TNF.

Table I. Demographic data and clinical features.

Reference	Type of study	Biologic drugs	Dosage	Paediatric Patients Disease subtypes; gender, Myositis specific Antibodies (number)	Clinical features at study (number)	Myositis specific antibodies or myositis associated antibodies (number)	Age at treatment in year (median; range)	Disease length in months (median; range)	Previous treatment (number)	Concomitant treatment (number)	Follow-up length in months (median; range)	Medication at last follow-up (number)
Cooper *et al*., 2007 (14)	Case Series	RITUXIMAB	375 mg/m2 /weekly for 4 weeks	3 JDM (2 F, 1 M);	Myositis (3), skin rashes (3)	Anti–Mi-2 (1)	14.1 (11-15.2)	4 (1.5 -27)	PDN (3), MTX (3), IVIG (2), CYC (1) HCQ (1), MPD (2)	PDN (2), MTX (3), IVIG (2), HCQ (1) MPD (2)	24 (12-26)	MTX (2) IVIG (1)
El Hallak *et al*., 2007 (15)	Case Series	RITUXIMAB	375 mg/m2 weekly for 4 weeks, repeated after 23 months	1 JDM (1 F)	Myositis, skin rash, calcinosis	NA	14	71	CYC, CYA, IVIG, PDN, MPD	CYC, IVIG, MTX	23	MTX, PDN
Dinh *et al*., 2007 (21)	Case Report	RITUXIMAB	375 mg/m2 /weekly for 4 weeks	1 JDM (1 F),	Skin rash	NA	16	96	PDN, HCQ, MTX, topical tacrolimus	CYA, topical steroid	33	None
Riley *et al*., 2008 (26)	Case Series	INFLIXIMAB	3 mg/kg (weeks 0-2-6 and every 8 weeks thereafter)	5 JDM (3 F, 2 M)	Myositis (5), skin rash (4) calcinosis (4), joint contractures (4)	NA	8.3 (6.25 – 8.8)	40 (24-52)	MTX (5), IVIG (2), CYA (3), CYC (3), HCQ (1), Corticosteroids (5), PMD (2), AZA (1)	MTX (5), PMD (5), HCQ (2), Corticosteroid (5), AZA (1), CYA (1), CYC (1)	24 (8-30)	MTX (5), PMD (5), HCQ (2), Corticosteroid (5), AZA (1), CYA (1), CYC (1)
Rouster-Stevens *et al*., 2008 (25)	Case series	INFLIXIMAB	3-3.5-4mg/kg	3 JIIM (3 F);	Myositis (3), ILD (2) Cardiac involvement (2)	anti-SRP (3)	14 (11-16)	18 (13-42)	PDN (3), MTX (3), IVIG (2), MMF (2), MPD (1), TAC (1), CYC (1), HCQ (1)	NA	6.3 (6-7)	CYA (1), MPD (1), NA (2)
Tzaribachev *et al*., 2009 (16)	Case Series	RITUXIMAB	375 mg/m2 /weekly for 4 weeks	1 JDM (1 F)	Myositis	NA	15	12	MPD, PDN, MTX, IVIG, CYA	MTX, IVIG, MPD	30	ASCT
Holzer *et al*., 2010 (17)	Case Report	RITUXIMAB	375 mg/m2 /weekly for 3 or 4 weeks	2 JDM (2 F)	Myositis (2), joint contractures (2)	NA	10.8 (8-13.6)	23 (18-28)	MPD (2), MTX (2), CYA (1), CYC (1), IVIG (1)	MTX (2), PDN (1), CYC (1), MPD (1)	32.5 (25-40)	ASCT (2)
Bader-Meunier *et al*., 2011 (18)	Case Series	RITUXIMAB	375 mg/m2 /weekly for 4 weeks (5 pts) 375 mg/m2 /weekly for 2 weeks (1 pt) 500 mg/m2 /weekly for 2 weeks (2 pts)	8 JDM (7 F, 1 M)	Myositis (6), skin rashes (6), calcinosis (6), gastrointestinal involvement (3), capillary leak syndrome (1)	Anti-Ku (1)	9.65 (6.1-16)	42.5 (1-100)	PDN (8), MPD (4), MTX (7), IVIG (2), CYC (1), CYA (6), MMF (2), AZT (1), TPE (3)	PDN (8), MTX (2). MMF (1), TPE (2), CYA (1)	39 (24-48)	
Green *et al*., 2014 (28)	Case Series	ETANERCEPT	NA	7 JDM (5 F, 2 M)	Myositis (7), skin rash (4)	NA	NA	35 (10-60)	PDN (7), MTX (7)	PDN (7), MTX (7)	20 (6-85)	NA

Rider *et al*., 2 014 (19)	Sub-analysis of RCT	RITUXIMAB	RTX at weeks 0, 1 and placebo at weeks 8, 9 (1 pt); placebo at weeks 0, 1 and rituximab at weeks 8, 9 (3 pt)	4 JDM (NA)	NA	Anti-TIF-1γ (2) Anti-NPX2 (1)	12.3 (9.9-16.9)	NA	NA	NA	11	NA
Rouster-Stevens *et al*., 2014 (27)	Case Series	ETANERCEPT	0.4mg/kg twice weekly	8 JDM (6 F, 2 M)	Myositis (8), skin rash (8)	NA	13.5 (7-18)	72 (39.6-129.6)	MPD (8), PDN (8), HCQ (8), MTX (7), CYC (1), CYA (1), IVIG (1)	MTX (8), HCQ (7), PDN (7), MPD (3), IVIG (1)	6	MTX (8), HCQ (7), PDN (7), MPD (3), IVIG (1)
Sun *et al*., 2015 (29)	Case Series	ETANERCEPT	NA	4 JDM (NA)	Myositis (4)	NA	NA	NA	NA	NA	16.5	NA
Binns *et al*., 2017 (20)	Case Report	RITUXIMAB	750 mg/m2, repeated 2 weeks later	3 JIIM (3 F);	Myositis (3), ILD (3)	anti-SRP (3)	13 (11-14)	4 (2-4)	MPD (3), MTX (3), PDN (3), CYC (1)	MTX (3), PDN (3), CYC (3)	10 (6-12)	MTX (3), IVIG (3) PDN (3), CYC (1)
Alhemairi *et al*., 2017 (23)	Case Series	RITUXIMAB	375 mg/m2 /weekly for 4 weeks	4 JDM (2 F, 2 M)	Myositis (4), calcinosis (4), skin rash (4), joint contractures (3)	NA	8.7 (6.5-9.6)	35 (30-38)	PDN (4), MTX (4); HCQ (4); IVIG (4); CYC (1); CYA (1); MMF (1); AZT (1); WFN (1); CC (2); PMD (3)	MTX (3); IVIG (1); PDN (4); HCQ (1); CYA (1); CYC (1)	42 (24-48)	NA
Tansley *et al*., 2017 (52)	Case Report	INFLIXIMAB (1) RITUXIMAB (2)	NA	JIIM (2 F, 1 M);	Myositis (3), skin rash (1)	anti-HMGCR (3)	NA	NA	MTX (3), PDN (2), MPD (1), AZA (1), CYC (1)	NA	6	NA
Aggarwal *et al*., 2017 (22)	Sub-analysis of RCT	RITUXIMAB	RTX at weeks 0, 1 and placebo at weeks 8, 9 (1 pt); placebo at weeks 0, 1 and rituximab at weeks 8, 9 (3 pt)	48 JDM (31 F, 17 M)	Skin rashes (48), calcinosis (22)	Anti-Mi-2 (5), Anti-NXP2 (16), Anti-TIF1 γ (13), anti-SAE (1), Anti-synthetase (1), others (3)	15.3	81.6	NA	PDN (36), AZA (5), MTX (38), IVIG (8), MMF (3), TAC (1) other (9)	11	PDN (36), AZA (4), MTX (38), IVIG (11), MMF (3), TAC (1)
De Guzman *et al*., 2017 (31)	Case Series	ABATACEPT	NA	4 JDM (3 F, 1 M)	Calcinosis (4)	NA	NA	NA	Na	IVIG (4), MTX (4), HCQ (4), PDN (4), MPD (4), RTX (2),	13.5 (10-32)	NA
Campanilho-Marques *et al*., 2020 (5)	large retrospective cohort study	INFLIXIMAB (39) ADALIMUMAB (4) INFLIXIMAB+ ADALIMUMAB (15)	IFX: 6 mg/kg every 4 weeks; ADA: 24 mg/m2 every 2 weeks	60 JDM (43 F, 17 M)	Calcinosis (28)	Anti-TIF1γ (19) Anti-NXP2 (7) Anti-MDA5 (1) Anti-Mi2 (1) Anti-SRP (1) Anti-PL-7 (1) Anti-HMGCR (1)	NA	37.2 (20.4-58.8)	MTX (48), AZA (48), HCQ (48), PDN (47), CYC (26), IVIG (5),	MTX (43), AZA (43), HCQ (43), PDN (26), CYC (3), IVIG (6),	12)	MTX (41), AZA (41), HCQ (41), PDN (26), IVIG (1)

NA: not available; MRI: magnetic resonance imaging; JDM: juvenile dermatomyositis; JIIMs: juvenile idiopathic inflammatory myopathies; CHAQ: Childhood Health Assessment Questionnaire; CMAS: Childhood Myositis Assessment Score; VAS: Visual Analogue Scale; MMT-8: manual muscle testing in 8 muscles; PedsQL: Paediatric Quality of Life Inventory; DAS: Disease Activity Score; GDA: global disease activity; Anti-SRP: anti-signal recognition particle; Anti-HMGCR: anti-hydroxy-metylglutaryl coenzyme A reductases; PDN: prednisone; MPD: methylprednisolone; MTX: methotrexate; IVIG: intravenous immunoglobulin; CYC: cyclophosphamide; CYA: cyclosporin A; HCQ: hydroxychloroquine; ASCT: autologous stem cell transplantation; PMD: pamidronate; CC: colchicine; WFN: warfarin; AZT: azathioprine; TPE: therapeutic plasma exchange; TAC: tacrolimus.

Table II. Main outcome measures and other data entered for each of the eligible studies assessing efficacy and safety of biologics on active myositis.

References	Type of study	Paediatric Patients Disease subtypes; gender, (Number)	Age at treatment in year (median; range)	Disease length in months (median; range)	Biologic drugs	Dosage	Outcomes	No Response (N. patients)	Partial Response (N. patients)	Complete Response (N. patients)	Complete clinical remission (N. patients)	Follow-up length in months (median; range)	Medication at last follow-up (number)	Adverse effects	GRADE quality assessment
Cooper *et al*., 2007 (14)	Case Series	3 JDM (2 F, 1 M);	14.1 (11-15.2)	4 (1.5 -27)	RITUXIMAB	375 mg/m2 /weekly for 4 weeks	Muscle strength, muscle enzyme	-	-	3	1	24 (12-26)	MTX (2) IVIG (1)	-	Very Low
El Hallak *et al*., 2007 (15)	Case Series	1 JDM (1 F)	14	71	RITUXIMAB	375 mg/m2 weekly for 4 weeks, repeated after 23 months	Muscle strength, Muscle enzyme	-	-	1	0	23	MTX, PDN	-	Very Low
Riley *et al*., 2008 (26)	Case Series	5 JDM (3 F, 2 M)	8.3 (6.25 – 8.8)	40 (24-52)	INFLIXIMAB	3 mg/kg (weeks 0-2-6 and every 8 weeks thereafter)	Muscle strength, muscle enzyme; CHAQ, CMAS, VAS	0	1	4	0	24 (8-30)	MTX (5), PMD (5), HCQ (2), Corticosteroid (5), AZA (1), CYA (1), CYC (1)	headaches during the first 3 infusions (1) infected calcinotic abscess (2)	Very Low
Rouster-Stevens *et al*., 2008 (25)	Case Report	3 JIIM (3 F)	13.6	22,3	INFLIXIMAB	3-3.5-4mg/kg	Muscle strength muscle enzyme	3	-	-	0	7	CYA (1), MPD (1), NA (2)	-	Very Low
Tzaribachev *et al*., 2009 (16)	Case Series	1 JDM (1 F)	15	12	RITUXIMAB	375 mg/m2 /weekly for 4 weeks	Muscle strength, muscle enzyme	1	-	-	0	30	ASCT	-	Very Low
Holzer *et al*., 2010 (17)	Case Report	2 JDM (2 F)	10.8 (8-13.6)	23 (18-28)	RITUXIMAB	375 mg/m2 weekly for 3 or 4 weeks	Muscle strength	2	-	-	0	32.5 (25-40)	ASCT (2)	-	Very Low
Bader-Meunier *et al*., 2011 (18)	Case Series	6 JDM (6 F)	9.1 (6.1-16)	30.5 (1-100)	RITUXIMAB	375 mg/m2 /weekly for 4 weeks (5 pts) 375 mg/m2 /weekly for 2 weeks (1 pt) 500 mg/m2 /weekly for 2 weeks (2 pts)	Muscle strength, muscle enzyme; MMT8	3	-	3	2	31.4		acute infusion-related event (1), GI perforation (1), Localised bacterial infection of the calcinosis sites (2)	Very Low

Green *et al.*, 2014 (28)	Case Series	7 JDM (5 F, 2 M)	NA	35 (10-60)	ETANERCEPT	NE	Muscle strength, CMAS	3	2	1	20 (6-85)		NA	Very Low	
Rider *et al.*, 2014 (19)	Sub-analysis of RCT	4 JDM (NA)	12.3 (9.9–16.9)	NA	RITUXIMAB	RTX at weeks 0, 1 and placebo at weeks 8, 9 (1 pt); placebo at weeks 0, 1 and rituximab at weeks 8, 9 (3 pt)	Muscle strength, MRI, MMT8, CMAS, VAS, PedsQL	-	4	-	0	11	NA	NA	Moderate
Rouster-Stevens *et al.*, 2014 (27)	Case Series	8 JDM (6 F, 2 M)	13.5 (7-18)	72 (39.6-129.6)	ETANERCEPT	0.4mg/kg twice weekly	Muscle strength; muscle enzymes; CMAS, DAS,	2	6	-	0	6	MTX (8), HCQ (7), PDN (7), MPD (3), IVIG (1)	-	Very Low
Sun *et al.*, 2015 (29)	Case Series	4 JDM (NA)	NA	NA	ETANERCEPT	NA	muscle strength; muscle enzyme	2	-	2	0	16.5	NA	-	Very Low
Binns *et al.*, 2017 (20)	Case Report	3 JIIM (3 F)	13 (11-14)	4 (2-4)	RITUXIMAB	750 mg/m2, repeated 2	Muscle strength, MMT8, CMAS weeks later	0	1	2	0	10 (6-12)	MTX (3), IVIG (3) PDN (3), CYC (1)	CMV pneumonia (1), bacterial abscess (1)	Very Low
Alhemairi *et al.*, 2017 (23)	Case Series	4 JDM (2 F, 2 M)	.7 (6.5-9.6)	35 (30-38)	RITUXIMAB	375 mg/m2 /weekly for 4 weeks	muscle strength, muscle enzymes	-	3	1	0	42 (24-48)	NA	generalised skin rash and hypotension (1), cellulitis (1) urinary tract infection (1), anaphylactic reactions (1) herpesvirus infection (1) pneumonia (1) sinusitis (1)	Very Low
Tansley *et al.*, 2017 (52)	Case Report	JIIM (2 F, 1 M);	NA	NA	INFLIXIMAB (1) RITUXIMAB (2)	NA	Muscle strength, Muscle enzyme	1 (RTX)	1 (RTX)	1 (IFX)	0	6	NA	-	Very Low

NA: not available; MRI: magnetic resonance imaging; JDM: juvenile dermatomyositis; JIIMs: juvenile idiopathic inflammatory myopathies. CHAQ: Childhood Health Assessment Questionnaire; CMAS: Childhood Myositis Assessment Score; VAS: Visual Analogue Scale; MMT-8: manual muscle testing in 8 muscles. PedsQL: Paediatric Quality of Life Inventory; DAS: Disease Activity Score; GDA: global disease activity; Anti-SRP: anti-signal recognition particle; Anti-HMGCR: anti-hydroxy-metylglutaryl coenzyme A reductases; PDN: prednisone; MPD: methylprednisolone; MTX: methotrexate; IVIG: intravenous immunoglobulin; CYC: cyclophosphamide; CYA: cyclosporin A; HCQ: hydroxychloroquine; ASCT: autologous stem cell transplantation; PMD: pamidronate; CC: colchicine; WFN: warfarin; AZT: azathioprine; TPE: therapeutic plasma exchange; TAC: tacrolimus.

Due to the limited number of patients treated with each anti-TNF and the heterogeneity of the data, we could not perform a head-to-head drug comparison.

During treatment with anti-TNF, 14 severe adverse events were reported (9 allergic reactions to IFX, 1 sepsis, 2 pneumonia, 2 infection of calcinosis). One patient died due to gastric perforation, but the event was referred by the authors to inflammatory complication of JIIM and not to anti-TNF treatment (30). Eighteen non-severe events were also reported (14 infection, 2 local injection site reaction, 1 transient headache during IFX infusion, and 1 skin rash).

The follow-up period for children receiving anti-TNF treatment was widely different across the eligible studies, ranging from a minimum of 6 month for a patient in the study by Rouster-Stevens *et al*. (27) to a maximum of 85 months in the study conducted by Green *et al*. (28); the median time was 12 months.

Other biological drugs

There are 4 patients treated with Abatacept for calcinosis in the study by De Guzman *et al*. (31). ABA was administered to 4 subjects with a dosage of 10 mg/ kg in weeks 0, 2, 4 and then every 4 weeks. The authors reported previous treatment with RTX in two of the patients. All patients had clinical and imaging improvement of calcinosis with resolution of pain, tenderness, and inflammatory changes at the sites of calcinosis. No severe side effects were reported during treatment.

Discussion

JIIMs represents a heterogeneous group of chronic inflammatory diseases characterised by a severe course in many patients. In JDM, the most common subtype of JIIM, the prognosis is variable, with a low overall mortality of 2–3%, and approximately 24–40% of patients having a monocyclic course, recovering with appropriate therapy within a 2-year period. However, the majority (50–60%) of patients with JDM experiences an chronic illness course (33, 34). The first-line treatment of JDM is based on the combination of DMARDs (*i.e*. methotrexate or cyclosporine) and glucocorticoids. Unfortunately, this approach is not always efficacy. In a randomised clinical trial Ruperto *et al*. have shown that at month 6, only 51% of the patients treated with prednisone and 70% of those on prednisone plus cyclosporine or on prednisone plus methotrexate showed a satisfactory clinical improvement (10).

Moreover, in this clinical trial JDM patients with severe ulceration of skin or vital organ involvement (gastrointestinal tract, heart, or lung) were not considered eligible. Thus, patients with more severe phenotypes, likely associated with anti-TIFy or anti-NPX2 MSA, were probably excluded from the study as MSA profile was not assess during the study.

Thus, the real-life efficacy of DMARD in JDM might be lower than the reported one and treatment of unresponsive patients to conventional treatment or with severe disease is challenging and several strategies have been attempted.

A prominent role as treatment for these patients is represented by intravenous immunoglobulin (IVIg). IVIg represent a safe and effective therapy for most subgroups of JIIMS since many years and they are often use in combination with other DMARDs to induce and maintain remission (35).

Other intensive immunosuppressive therapies such as azathioprine, mycophenolate mofetil, and tacrolimus, have been used, especially in severe patients. In patients with life-threating complication, the use of intravenous cyclophosphamide, plasma exchange or autologous stem cell transplantation is advocated (36), even in paediatric age (37, 38).

Biologic agents have been used in patients with inflammatory myositis since few years. However, in a recent survey by Childhood Arthritis and Rheumatology Research Alliance (CARRA), more than half of the responders, reported the use of one or multiple biologic agents in JDM, suggesting a role for RTX, ABA, tocilizumab and anti-TNF-α agents in refractory JDM (39). Moreover, the response to medication was based on expert opinion and not evidence derived; up to now no study has summarised the current available evidence regarding efficacy and safety of the biologics in JIIMs.

Thus, the aim of our systematic review was to identify all studies enrolling paediatric patients with JIIMs, treated with biologic agents, retrieving data from published papers from 1975 to 2020.

We limited our analysis to childhood age, but paediatric data could not be extracted from the only randomised, double-blind, placebo-phase controlled clinical trial involving both JDM and adult dermatomyositis, since they have been reported in aggregated way (32). We contacted authors to determine whether information was specifically available on children to allow the study to be included, but the required data were not extractable form the original data set. This did not result in any additional study being eligible. The main outcome of the study was defined according to IMACS response criteria as ≥20% improvement in 3 of any 6 core set measures, with no more than 2 worsening by ≥25%. The MMT could not be one of the worsening measures (40).

This trial reports that RTX induces disease improvement in more than 80% of enrolled patients, along with a significant steroid tapering over time (32). Moreover, by a *post-hoc* multivariate analysis Aggarwal *et al*. demonstrated that JDM was associated with a better and more rapid response to RTX, in comparison to adult dermatomyositis (41). The presence of the MSA anti-Mi-2 was associated with a better response to RTX; these are reported in 3–4% of patients with JDM. The same study reported a better outcome when RTX was administered to patients with lower myositis related damage; this findings in line with the study by Bader-Meunier *et al*. which reported that responders to RTX had a shorter disease duration (<3.5 yrs.) than non-responders (18).

Taking into account these data along with the CD20 B-cell key role in driving muscular damage pathogenesis (42), RTX, the most common CD20 B cell-depleting monoclonal antibody, represents an appealing and reasonable choice in treating JIIMs. Nonetheless, the evidence coming from this systematic review, in our opinion, shows that RTX remains a valuable treatment option.

Table III. Main outcome measures and other data entered for each of the eligible studies assessing efficacy and safety of biologics on skin manifestations.

References	Type of study	Pediatric Patients Disease subtypes; gender	Age at treatment in year (median; range)	Disease length in months (median; range)	Biologic drugs	Dosage	Skin vasculitis			Calcinosis			Complete clinical remission (N. patients)	Medication at last follow-up (number)	Follow-up length in months (mean; range))	Adverse effects	GRADE quality assessment
							No Response (N. patients)	Partial Response (N. patients)	Complete Response (N. patients)	No Response (N. patients)	Partial Response (N. patients)	Complete Response (N. patients)					
Dinh *et al.*, 2007 (21)	Case Report	1 JDM (1 F),	16	96	RITUXIMAB	375 mg/m2 /weekly for 4 weeks	-	-	1	-	-	-	0	None	33	-	Very Low
Cooper *et al.*, 2007 (14)	Case Series	4 JDM (3 F, 1 M)	14,5 (10,83-17,75)	2.5 (1,5 -27)	RITUXIMAB	375 mg/m2 /weekly for 4 weeks	1	1	2	-	-	-	1		19 (12-26)	-	Very Low
Riley *et al.*, 2008 (26)	Case Series	5 JDM (3 F, 2 M)	7,2	36,8	INFLIXIMAB	3 mg/kg (weeks 0-2-6 and every 8 weeks thereafter)	-	1	4	1	3	-	0		18,4 (8,12,18, 24,30)	headaches during the first 3 infusions (1) infected calcinotic abscess (2)	Very Low
Bader-Meunier *et al.*, 2011 (18)	Case Series	8 JDM (7 F, 1 M)	9,65 (6,1-16)	42.5 (1-100))	RITUXIMAB	375 mg/m2 /weekly for 4 weeks (4 pts) 375 mg/m2 /weekly for 2 weeks (1 pt) 500 mg/m2 /weekly for 2 weeks (2 pts)	2	-	3	6	-	-	0		39 (24-48)	acute infusion-related event (1), GI perforation (1), Localised bacterial infection of the calcinosis sites (2)	Very Low
Rouster-Stevens *et al.*, 2014 (27)	Case Series	8 JDM (6 F, 2 M)	13.5 (7-18)	72 (39.6-129.6)	ETANERCEPT	0.4mg/kg twice weekly	2	5	-	-	-	-	0		6	-	Very Low
Alhemairi *et al.*, 2017 (23)	Case Series	4 JDM (2 F, 2 M)	7,1	20	RITUXIMAB	375 mg/m2 /weekly for 4 weeks	NA	NA	NA	0	3	1	0		39	generalised skin rash and hypotension (1), cellulitis (1) urinary tract infection (1), anaphylactic reactions (1) herpesvirus infection (1) pneumonia (1) sinusitis (1)	Very Low
Aggarwal *et al.*, 2017 (22)	Sub-analysis of RCT	48 JDM (31 F, 17 M)	15,3	81,6	RITUXIMAB	RTX at weeks 0, 1 and placebo at weeks 8, 9 (1 pt); placebo at weeks 0, 1 and rituximab at weeks 8, 9 (3 pt)	5	28	15	22	0	0	NA	PDN (36), AZA (4), MTX (38), IVIG (11), MMF (3), TAC (1)	11	-	Moderate
De Guzman *et al.*, 2017 (31)	Case Series	4 JDM (3 F, 1 M)	NA	NA	ABATACEPT	NA	-	-	-	-	.-	2	NA	-NA	13.5 (10-32)		Very Low
Campanilho-Marques *et al.*, 2020 (5) study	Large retrospective cohort	60 JDM (43 F, 17 M)	8.3	37.2 (20.4- 58.8)	INFLIXIMAB (39) ADALIMUMAB (4) INFLIXIMAB+ ADALIMUMAB (15)	IFX: 6 mg/kg every 4 weeks; ADA: 24 mg/m2 every 2 weeks	NA	NA	NA	6	7	8	NA	MTX (41), AZA (41), HCQ (41), PDN (26), IVIG (1),	12	allergic reactions to IFX (9), sepsis (1) pneumonia (2) Gastric perforation (1) infection, (14) local injection site reaction (2) skin rash (1).	Low

NA: not available; MRI: magnetic resonance imaging; CMAS: Childhood Myositis Assessment Score; VAS: Visual Analogue Scale; MMT-8: Manual Muscle Testing in 8 muscles; PedsQL: Paediatric Quality of Life Inventory; DAS: Disease Activity Score.

According to our systematic review, anti-TNF agents represent the most common type of biologic agents used in JJIIMs, and in JDM specifically.

However, we also could not extract data on efficacy on skin vasculitis and myositis from the largest study conducted since now on anti-TNF-α. Campanilho-Marques *et al*. reported data as aggregated and no data regarding each single patient were available. Efficacy of the medication was reported as an improvement of 4 Core outcome variables for JDM proposed by IMACS (CMAS, Manual Muscle Testing of 8 groups, physician's global assessment of disease activity, modified Disease Activity Score as a measure of skin disease activity) (30).

According to these retrospective studies, anti-TNF agents result in an improvement both on skin vasculitis and active myositis. Moreover, in treated patients a reduction in steroid dose was also achieved.

Campanilho-Marques *et al*. also suggested a drug-specific action for each anti-TNF-α, with a limited role of ETA in treating JIIMs. Indeed, it is well-known from other diseases that ETA might not show the same action as IFX or ADA (43). Moreover, even if in our study a head-to-head drug comparison was not possible due to the limited data, ETA showed a reduced efficacy on muscle inflammation with only 16% of treated patients reaching complete clinical response also in our analysis.

As calcinosis is a severe complication of JDM responsible of a high functional impairment and no treatment is still defined (44), treatment with IFX or ADA might be useful in patients with calcinosis.

Anti-TNF agents might reduce the pre-existing lesions or preventing the development of new ones. According to the study from Campanilho-Marques *et al*., a prolonged exposure to the medications is required as continuous treatment for nearly 2 years is necessary to get reduction in the number and size of calcinosis (30).

The role for other biologic agents in JIIM is even more conflicting and not supported by evidence, despite the wide use reported by paediatric rheumatologists interviewed in the CARRA study (39). Abatacept has been reported as efficacious on calcinosis, but a previous treatment with RTX in two of the patients might have contributed, at least in part, to the favourable outcome of the patients (31). A clinical trial is ongoing (ClinicalTrials.gov Identifier: NCT02594735) and might further clarify its role in JIIMs.

No studies on tocilizumab have been included in this analysis. At the time of this systematic review, only a single case report was reported about a child with overlap syndrome and predominant muscle involvement. The anti-IL6 agent was used to treat arthritis while skin vasculitis and myositis were in remission (45).

We acknowledge that this systematic review has several *caveats* and limitations, mainly related to the number, quality, and design of the analysed studies. The result of this systematic review is based on publications of non-controlled trials/case series, retrospective in most cases. Aside from the RIM trial, however, no studies including children and adults compare data with a control group. Additionally, patients received additional treatments in a very heterogeneous way from one publication to another.

From most of the studies the proportion of patients with complete clinical response was obtained relying to clinical judgement. The different used outcome measures resulted not directly comparable, and the follow-up periods ranged widely. These further limitations prompted us to not perform a statistical analysis of the retrieved data, and rather to simply describe the obtained results.

A major limitation is the wide heterogenicity in the definition of clinical response, since only few studies adopted an international validated definition of clinical response or clinical remission.

The majority among the eligible studies adopted the definition of as for the treating physician judgment, and, of course, it is not an objective outcome measure. Additionally, even when a standardised definition is used, they are not consistent and reliable each other, as they consider different items. In this clinical setting, PRINTO criteria defined complete remission as a Childhood Myositis Assessment Scale of ≥48, the absence of skin disease and a Physician's Global Assessment Score of <1 (46); differently, the International Myositis Assessment and Clinical Studies Group defined complete clinical response as no evidence of active myositis for 6 months while receiving medications, and complete clinical remission as no evidence of active myositis for 6 months without receiving medications (13). In 2016 the American College of Rheumatology/European Leagues Against Rheumatism defined common criteria for defining improvement in JDM (47); however, till now, no study on biologic agents in JDM adopted such composite criteria to define response. Thus, combining the different main outcome measures to define a response item to the drug was otherwise the only available measure for assessing differences in JIIMs, and thus to date, the only item able to compare different studies, across different decades and different JIIM diseases.

Another limitation is the wide heterogenicity of disease length at the time of biologic administration; as reported above for RTX, an early treatment administration might induce a better response and prevent the development of permanent sequelae and disability. Thus, study designs including homogeneous population with regard to disease damage score and disease length would be useful to clarify this issue.

Moreover, a refractory disease, defined according to the definition adopted by the RIM trial ("the intolerance to or an inadequate response to glucocorticoids and at least one other immunosuppressive or immunomodulatory agent"), was the main indication for the use of biologic agents in most of these studies; thus, these patients showed a wide variability in terms of previous or concomitant treatment, including DMARDs, corticosteroid and other (*i.e*. plasma exchange, pamidronate). For example, in the study from Campanilho-Marques *et al*., 80% of patients received ≥2 DMARDs before biologic agents and in 50% anti-TNF-α were used in combination with ≥2 other medication, excluding corticosteroids.

Therefore, the cumulative effect of such sequential treatment could contribute to determining the overall efficacy of biologic agents. On the other hand, we might speculate that earlier use of biologic agents after accurate patient selection might result in higher efficacy of such medication, following the "windows of opportunity hypothesis" elaborated for rheumatoid arthritis (48), and thus in a reduced burden of disease complication.

However, in absence of higher-quality studies, we had to accept open-label studies, retrospective cohorts, and case series and outline the poor quality of evidence. The results of this systematic review measured the current available evidence of the biologic therapy in JIIMs, thus highlighting the no solid evidence of their current use and the urgent need of RCTs and, overall, more robust evidence in this clinical setting.

Due to the limited number of patients and the overall very low quality of the available studies, we could not adopt a meta-analysis approach to directly compare different treatments, including the most representative approaches, RTX and anti- TNF-α. The very low-quality data could have hampered the definitive conclusions drawn about reciprocal drug comparisons.

In conclusion, we fully recognise the generally poor quality of evidence due to the availability of eligible studies and the inherent selection bias of this analysis. The results of this review could be anyway helpful for clinicians in judging the utility of the available treatments and their side effects on JIIM prognosis, as well as in making a therapeutic decision based on current available evidence. Since the present evidence arises from retrospective observational studies, multicentre RCTs are still urgently needed to determine optimal treatment protocols in childhood-onset JIIMs. Additional data are promptly required from the JIIM research groups to clarify the exact role of the current available spectrum of treatment and to unveil a different response related to the type of used drug. The recent insights in the pathogenic role of myositis-specific autoantibodies, genetic factors, and type 1 interferon pathways, should drive a better stratification of patients according to specific disease clusters. This process might therefore contribute to a better tailoring of candidate treatment. In the future, the choice between DMARDs, biologic agents, as well as other promising agents, as JAK-inhibitors (49-51) might be differentiated from one cluster, showing homogeneity in terms of clinical presentations, disease complications and overall prognosis, to another. In such complicated scenario, the choice of biologics or small molecules in JIIM patients might also lead by disease stratification and peculiarities, rather than always by a step-up approach based on steroid plus one/several non-biologic DMARD.

JIIMs, and specifically JDM, are of course challenging and life-threating diseases that deserve high quality of evidence for appropriate therapeutic decisions. According to this systematic review, JIIMs do not currently have the proper evidence-based treatment they need.

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