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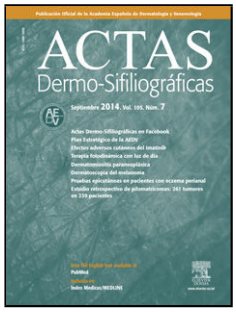

RF - New treatments in dermatomyositis: present and future

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Sección. Foro para Residentes

RF - New treatments in dermatomyositis: present and future

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Dermatomyositis is an autoinflammatory and autoimmune disease that primarily affects the skin and striated muscle. It may also involve the lungs and can be complicated by calcinosis. Despite its considerable morbidity and the significant impact on quality of life, IV immunoglobulin (IVIg) remains the only treatment approved to date by the US Food and Drug Administration (FDA). This approval was based on a phase III, placebo-controlled clinical trial published in 2022 that included 95 patients. In that study, 79% of patients treated with IVIg (2 g/kg every 4 weeks for 16 weeks) achieved improvement in the Total Improvement Score (TIS) vs 44% in the placebo group ($p < 0.001$). Moreover, more than 70% of patients achieved at least a 35% improvement in the Cutaneous Dermatomyositis Activity and Severity Index–Activity (CDASI-A) score at week 28. However, patients with predominantly cutaneous disease were excluded, limiting the generalizability of these findings to this subgroup.[1] In clinical practice, IVIg is generally reserved for severe disease refractory to corticosteroid therapy. Beyond IVIg, pharmacologic management typically includes glucocorticoids as first-line therapy, often combined with immunosuppressants such as azathioprine, methotrexate, and mycophenolate mofetil to improve efficacy and reduce steroid dependence.

Recently, 3 working groups have reviewed current and emerging therapies for dermatomyositis, with particular emphasis on the cutaneous domain. A summary of these treatments, their mechanisms of action, and clinical outcomes is shown in Table 1.[2–4]

Broadly, these therapies act on 3 major targets: T lymphocytes, B lymphocytes, and the Janus kinase (JAK)–interferon pathway.[2–4] Abatacept, a T-cell costimulation inhibitor, has demonstrated efficacy in both muscular and cutaneous signs of dermatomyositis, including juvenile and adult-onset disease. However, other case reports describe poor response to this agent, leaving its overall effectiveness uncertain.[2]

Regarding B lymphocytes, rituximab (anti-CD20) has shown heterogeneous results. Although the RIM trial did not find significant differences in time to improvement between early- and late-rituximab groups ($p = 0.74$), subgroup analysis revealed significant improvement in cutaneous activity in both adults and children with dermatomyositis. Moreover, these improvements were superior when compared with cyclophosphamide.[2] Additionally, several recent reports describe successful treatment with CAR-T (chimeric antigen receptor T-cell) therapy in patients with refractory

antisynthetase syndrome,[3–4] a condition considered by many authors to fall within the dermatomyositis spectrum, opening the door to future use of these therapies. Belimumab, a selective inhibitor of BLyS (B-cell activating factor, BAFF), has also shown potential efficacy: in a recent series of 13 patients with dermatomyositis or juvenile dermatomyositis, clinical responses—cutaneous and muscular—were observed in more than 80% of cases.[5]

Furthermore, the JAK–STAT–interferon axis plays a key role in the pathogenesis of dermatomyositis. Favorable responses have been described with various JAK inhibitors, particularly tofacitinib and baricitinib.[2–4] Similarly, several isolated case reports have documented responses to anifrolumab, a type I interferon receptor subunit 1 inhibitor, in both juvenile and adult dermatomyositis.[3–4] Currently, 3 clinical trials are underway in dermatomyositis: baricitinib (NCT05524311, phase II), anifrolumab (NCT06455449, phase III), and dazukibart (NCT06698796, phase III), the latter targeting interferon-β.[3–4]

Finally, apremilast, a phosphodiesterase-4 inhibitor, has shown possible efficacy in dermatomyositis, with overall response rates > 80% in CDASI-A scores in a recent phase II trial at a dose of 30 mg twice daily.[6] Its efficacy has been proposed in paraneoplastic dermatomyositis.[7]

Calcinosis in dermatomyositis remains a particularly challenging complication with multiple therapeutic options described—including diltiazem, low-dose warfarin, bisphosphonates (alendronate, pamidronate), colchicine, IVIg, intralesional corticosteroids, and sodium thiosulfate—but without consistent efficacy. Responses have been reported with infliximab or hematopoietic stem cell transplantation, especially in small and early lesions. Surgery is an option for symptomatic, refractory lesions, and very rarely, spontaneous regression may occur.[8]

In clinical practice, treatment selection depends on the predominant domain (cutaneous, muscular, pulmonary), refractoriness to corticosteroids and classic immunosuppressants, and the availability of advanced therapies. Thus, IVIg is typically reserved for severe, multisystemic, refractory disease. In refractory cutaneous involvement, JAK inhibitors such as tofacitinib or baricitinib—which are readily available and show favorable CDASI outcomes—may be considered, while interferon pathway inhibition with anifrolumab or dazukibart may represent future options pending completion of ongoing trials, with anifrolumab already showing promising results in case series. In patients with prominent muscular involvement, abatacept or belimumab may be viable immunomodulatory alternatives. In cases of suspected B-cell–driven disease or pulmonary involvement (eg, antisynthetase syndrome), rituximab or even anti-CD19 CAR-T therapy could be options in highly specialized settings. Finally, apremilast—with promising results in phase II trials—may be useful in predominantly cutaneous forms, including paraneoplastic disease. Despite meaningful advances, many of these therapies remain unapproved, and their use must therefore be individualized and considered primarily in refractory settings or within clinical trials.

With expanding knowledge on the pathophysiology of dermatomyositis, several new therapeutic agents are expected to be approved in the coming years for this orphan disease, particularly from a dermatologic standpoint.

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Table 1. New Drugs for the Treatment of Dermatomyositis Source: based on data from Bax C et al.[2], Kim H[3], Kim HJ et al.[4], and clinicaltrials.gov. Authors' own compilation.

Class	Drug	Specific Mechanism of Action	Clinical Trial or Reference Study*	Level of Evidence **	Endpoints	Main Dermatologic Outcomes	Evidence of Effectiveness in Cutaneous Dermatomyositis ***	Current Status in Dermatomyositis
T-cell inhibitors	Tocilizumab	IL-6 receptor inhibitor	Clinical trial	4	Evaluate the safety and efficacy profile of tocilizumab in refractory DM and PM	No improvement vs placebo	No	Not used
	Abatacept	CD80/86 inhibitor preventing ligand binding to CD28	Clinical trial	2	Evaluate the safety and efficacy profile of abatacept in refractory DM and PM	Improvement in muscular and dermatologic outcomes (CDASI)	Possible	Available target (frequently used)
	Rituximab	IL-20 inhibitor	Clinical trial	2	Evaluate the safety and efficacy profile of rituximab in refractory DM and PM	Initial trial showed dermatologic improvement, but later not confirmed	Contradictory	Available target (frequently used)
	Obinutuzumab	IL-20 inhibitor	Single case report	4	Evaluate the safety and efficacy profile of obinutuzumab in a patient with antisynthetase syndrome refractory to rituximab	Improvement in cutaneous and extracutaneous domains	Possible	Available target (rarely used)
B-cell inhibitors	Daratumumab	CD38 inhibitor	Case series (3 patients)	4	Evaluate the safety and efficacy profile of daratumumab in two DM and one PM patient	Improvement in cutaneous and extracutaneous domains	Possible	Available target (rarely used)
	Belimumab	BLyS inhibitor	Case series (13 patients)	4	Evaluate the safety and efficacy profile of belimumab in DM and juvenile DM	Improvement in cutaneous and muscular domains	Possible	In clinical trial (NCT02347891)
	Autologous anti-CD19	CD19 inhibitor	Case series (5 patients)	4	Evaluate the safety and	Improvement in cutaneous	Yes	Available target (rarely used)

Class	Drug	Specific Mechanism of Action	Clinical Trial or Reference Study*	Level of Evidence **	Endpoints	Main Dermatologic Outcomes	Evidence of Effectiveness in Cutaneous Dermatomyositis ***	Current Status in Dermatomyositis
	CAR-T therapy				efficacy profile of anti-CD19 CAR-T therapy in antisynthetase syndrome	and extracutaneous domains		
	Autologous anti-BCMA CAR-T therapy	BCMA inhibitor	Single case report	4	Evaluate the safety and efficacy profile of anti-BCMA CAR-T therapy in immune-mediated necrotizing myopathy	Improvement (no reference to cutaneous domain)	Possible	Available target (rarely used)
	IVIg	Ig receptor inhibitor	Randomized clinical trial	1	Evaluate the safety and efficacy profile of IVIg vs placebo in DM	Improvement in cutaneous (CDASI and others) and extracutaneous domains	Yes	Available target (frequently used)
IV immunoglobulins and FcRn inhibitors	Efgartigimod	FcRn inhibitor	NCT05669014 (phase II/III)	Pending	Evaluate the safety and efficacy profile of efgartigimod in DM, PM, and antisynthetase syndrome	Pending	Pending	Ongoing trial
	Nipocalimab	FcRn inhibitor	NCT05379634 (phase II)	Pending	Evaluate the safety and efficacy profile of nipocalimab in DM, PM, and antisynthetase syndrome	Pending	Pending	In trial
	Ruxolitinib	Dual JAK1/JAK2 inhibitor	Single case report	3	Evaluate the safety and efficacy profile of ruxolitinib in refractory DM	Improvement in cutaneous (CDASI) and extracutaneous domains	Yes	Available target (occasionally used)
	Tofacitinib	Pan-JAK inhibitor	Case series (10 patients)	3	Evaluate the safety and efficacy profile of tofacitinib in refractory DM	Improvement in cutaneous (CDASI) and extracutaneous domains	Yes	Available target (occasionally used)

Class	Drug	Specific Mechanism of Action	Clinical Trial or Reference Study*	Level of Evidence **	Endpoints	Main Dermatologic Outcomes	Evidence of Effectiveness in Cutaneous Dermatomyositis ***	Current Status in Dermatomyositis
JAK/STAT and interferon-pathway blockers	Baricitinib	Dual JAK1/JAK2 inhibitor	Case series (3 patients)	3	Evaluate the safety and efficacy profile of baricitinib in refractory DM	General improvement in cutaneous (CDASI) and extracutaneous domains	Yes	Available target (occasionally used); phase II trial ongoing in France (NCT05524311)
	Brepocitinib	Dual JAK1/TYK2 inhibitor	NCT05437263 (phase III)	Pending	Evaluate the safety and efficacy profile of brepocitinib in DM	Pending	Pending	Ongoing trial
	Anifrolumab	Type I interferon receptor subunit 1 inhibitor	Case series (4 patients)	3	Evaluate the safety and efficacy profile of anifrolumab in refractory DM	Improvement in cutaneous (CDASI and others) and extracutaneous domains	Yes	Available target (occasionally used); phase III trial ongoing (NCT06455449)
	Dazukibart	IFN-β inhibitor	Phase II clinical trial completed (NCT03181893)	Pending	Evaluate the safety and efficacy profile of dazukibart in refractory DM	Improvement in cutaneous, muscular, and internal domains	Pending phase III	In phase III trial (NCT06698796)
Antioxidants and mitochondrial oxidative-stress modulators	NAC	Antioxidant, ROS scavenger	Preclinical study	Pending	Evaluate relationship between NAC and interferon signature	NAC downregulates interferon-related gene expression	Possible	Available target (rarely used)
	Metformin	Mitochondrial complex I inhibitor	Preclinical trial	Pending	Evaluate relationship between metformin and NETs	May reduce NETs and innate immune response	Possible	Available target (rarely used)
	Enpatoran (M5049)	TLR7/8 inhibitor in dendritic cells	NCT05650567 (phase II)	Pending	Evaluate the safety and efficacy profile of brepocitinib in PM and DM	Pending	Pending	Ongoing trial
Others	Lenabasum	Cannabinoid receptor 2 inhibitor	Clinical trial	Pending	Evaluate the safety and efficacy profile of lenabasum in DM	Phase III results similar to placebo, which is why it is not recommended	No	Not used
	Apremilast	Phosphodiesterase-4 inhibitor	Non-randomized clinical trial	2	Evaluate the safety and efficacy profile of	Overall CDASI response rate > 85%	Yes	Not used

Class	Drug	Specific Mechanism of Action	Clinical Trial or Reference Study*	Level of Evidence **	Endpoints	Main Dermatologic Outcomes	Evidence of Effectiveness in Cutaneous Dermatomyositis ***	Current Status in Dermatomyositis
					apremilast in DM			

BCMA: B-cell maturation antigen; BLyS/BAFF: B-cell activating factor; CDASI: Cutaneous Dermatomyositis Disease Area and Severity Index; CAR-T: Chimeric Antigen Receptor T-cell therapy; CD: cluster of differentiation; DM: dermatomyositis; FcRn: neonatal Fc receptor; IFN: interferon; IL: interleukin; IVIg: intravenous immunoglobulin; JAK: Janus kinase; NAC: N-acetylcysteine; NET: neutrophil extracellular traps; PM: polymyositis; ROS: reactive oxygen species; TLR: Toll-like receptor; TYK: tyrosine kinase 2.

* Most advanced and/or dermatology-relevant trials/studies selected.

** According to 2011 Oxford Levels of Evidence.

*** Based on authors' assessment considering published literature and disease pathophysiology.

Source: based on data from Bax et al.[2], Kim H[3], Kim HJ et al.[4], and clinicaltrials.gov. Author's own elaboration.