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Etanercept as Steroid-Sparing Agent in Dermatomyositis

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We read with interest the paper by the Muscle Study Group, published in *Annals of Neurology*.[1] The authors concluded that there are no major safety concerns regarding the use of etanercept in dermatomyositis, and a steroid-sparing effect deserves further investigation.[1]

TABLE: Clinical Characteristics of Reported Patients Who Developed PM/DM during Anti–TNF-α Therapy

First Author, Year	Number of Patients (age, sex)	Baseline Diagnosis	Duration of Illness until Anti-TNF-α Initiation	Anti-TNF-α Therapy	Duration of Anti–TNF-α Therapy until Diagnosis of DM/PM	Autoantibodies before Anti–TNF-α Therapy	Autoantibodies after Anti–TNF-α Therapy	Improvement after Withdrawal of Anti–TNF-α Therapy, Treatment and Outcome
Musial, 20034,5	1 (52 yr, F)	RA	20 yr	Infliximab	30 mo	ANA 1 320, dsDNA neg, Jo-1 pos	ANA 1 320, dsDNA 1 20, Jo-1 pos	Yes, corticosteroids
Flendrie, 20034,5	1 (NA)	RA	NA	Infliximab	NA	NA	NA	NA
Flendrie, 20054,5	1 (52 yr, F)	RA	NA	Lenercept	2.5 mo	NA	NA	Yes, NA
Urata, 20064,5	1 (52 yr, F)	RA + pulmonary fibrosis	33 yr	Infliximab	9 mo	ANA1 640, dsDNA neg, Jo-1 pos	ANA 1 640, dsDNA neg, Jo-1 pos	Yes, corticosteroids
Hall, 20064,5	1 (44 yr, F)	Seronegative RA	1 yr	Etanercept	6 mo	ANA neg	ANA 1 640, dsDNA NA, Jo-1 pos	Yes, corticosteroids
Liozon, 20074,5	1 (47 yr, F)	RA	6 mo	Adalimumab	9 mo	ANA1 640, dsDNA pos, Jo-1 NA	ANA 1 2560, dsDNA pos, Jo-1 NA	Yes, corticosteroids
Kiltz, 2008,4,5	2 (46 yr, M)	AS	17 yr	Infliximab	3 mo	ANA neg	ANA neg	Yes, corticosteroids
	(57 yr, F)	RA	26 yr	Etanercept	30 mo	ANA 1 160	ANA 1 2,560	No, fatal outcome
Ramos-Casals, 20084,5	4 (NA)	RA	NA	Infliximab, etanercept, lenercept	NA	NA	NA	NA
Brunasso, 20104	1 (45 yr, F)	RA	13 yr	Adalimumab	34 mo	ANA neg	ANA 1 320, Jo-1 neg	Yes, corticosteroids
Klein, 20103	3 (40 yr, F)	RA	NA	Etanercept	2 yr	NA	ANA pos, dsDNA neg, Jo-1 neg	Partial improvement, corticosteroids, recurrence after 8 mo
	(29 yr, F)	Seronegative arthritis with familiar history of psoriasis	NA	Adalimumab	3 mo	NA	ANA 1 640, dsDNA neg, Jo-1 neg	Yes, corticosteroids + methotrexate + azathioprine + quinacrine
	(51 yr, F)	RA	NA	Adalimumab	2 mo	NA	NA	Yes, corticosteroids
Ishikawa, 20115	1 (52 yr, F)	RA + NSIP	2 yr	Etanercept	2 mo	ANA pos, dsDNA neg, Jo-1 pos	ANA 1 320, dsDNA neg, Jo-1 pos	Yes, corticosteroids

ANA = antinuclear antibodies; AS = ankylosing spondylitis; DM = dermatomyositis; dsDNA = double-stranded DNA; F = female; M = male; NA = not available; neg = negative; NSIP = nonspecific interstitial pneumonia; PM = polymyositis; pos = positive; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

We would like to underline that the skin involvement may be the most active component of dermatomyositis, imposing an important impairment of quality of life. Unfortunately, the authors did not consider the cutaneous disease activity score index (CDASI) as a relevant measure of the disease activity, not only because the skin response was not included in the treatment failure parameters, but also because there was no discussion regarding the absence of significant differences in CDASI between the treatment groups ($p = 0.23$ at week 24, $p = 0.17$ at week 52). Therefore, considering these results and that 5 patients receiving etanercept experienced worsened skin rash and 1 case even improved after withdrawal, we should be aware that etanercept might not be efficacious for the whole spectrum of dermatomyositis (skin and muscles). In addition, we should not forget that there are approximately 42 other cases reported in the literature regarding the use of anti-tumor necrosis factor (TNF) α agents in patients affected by dermatomyositis or polymyositis.[2,3] In 13 (31%) of those cases, a worsening of the disease was reported, and in 9 patients (21%) the onset of severe adverse events directly related to the TNF-α blockage forced the withdrawal of the drug, including 2 fatal cases.[2,3] Another interesting finding pertains to the paradoxical onset of dermatomyositis or polymyositis in patients treated with TNF-α antagonists mainly for rheumatoid arthritis (15 cases).[3–5] In total, 17 such cases are retrievable[3–5] (Table).

TNF-α blockage may induce autoimmune phenomena in individuals with some genetic background, as confirmed by the onset of autoantibodies (50% of antinuclear antibodies and 15% of anti-DNA antibodies), drug-induced lupus, vasculitis, antiphospholipid syndrome, and other autoimmune entities.[3–5] Anti–TNF-α therapy inhibits the cytotoxic T lymphocyte response that would normally suppress the autoreactive B-cell response, promoting humoral autoimmunity and increasing the type I interferon system, which has been implicated in the pathogenesis of dermatomyositis and polimyositis.[3–5]

To consider etanercept a valid steroid-sparing agent in patients with dermatomyositis, we need a clear positive benefit/damage ratio, which should be higher in comparison with other immunosuppressive agents (methotrexate, etc), considering the high economic impact of continuous therapy for 52 weeks as described in the aforementioned study.

Potential Conflicts of Interest

Nothing to report.

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Reply

Anthony A. Amato, MD, for the Muscle Study Group

We appreciate Dr Brunasso and colleagues' interest in our paper[1] and their concern that we did not properly assess skin manifestations of dermatomyositis (DM) because change in the cutaneous disease activity score index (CDASI) was not used as a criterion assessing for treatment failures. We agree and are keenly aware that skin activity may be the most active component of the DM, and this is why we employed several tools to assess dermatological manifestations. The International Myositis Assessment Clinical Study Group (IMACS) proposed a core set of measures for disease outcome assessment and preliminary definitions of improvement (DOI) to be used in clinical trials in myositis.[2–4] For definition of worsening, we took changes in the opposite direction of the DOI. In regard to skin manifestations, IMACS recommends using the skin-relevant components of the Myositis Disease Activity Assessment Tool (MDAAT). In addition to using the MDAAT, we also performed the CDASI, and subjects graded their pruritis using a visual analog scale. Skin involvement was also taken into account in the Physician and Patient Global Activity scores and patient quality of life scores.

A major aim of the study was to assess and compare various outcome measures in terms of their reliability and responsiveness. The CDASI, as mentioned in our paper, showed excellent intrarater reliability but was not very responsive. Nevertheless, utilizing various measures, we were able to demonstrate that 5 subjects on etanercept had worsening rash, 1 of whom did indeed meet the definition of worsening solely because of the worsening rash.

We are also aware of the possible autoimmune side effects of etanercept and mentioned this in our paper. One needs to exercise caution, however, in lumping together DM with polymyositis (PM) as Drs Brunasso and colleagues have done in their letter. DM, PM, and perhaps even the overlap myositides have distinct pathogenic bases. Drugs that help or worsen DM may not help or worsen PM and vice versa. We absolutely agree, and our findings support that the response to etanercept or any drug for that matter is quite variable in individual patients. Again, among the aims of our pilot study was to preliminarily assess the safety of etanercept in DM before