TIF1-gamma IgG2 isotype is not associated with malignancy in juvenile dermatomyositis patients

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Dear Editor,

The disease presentation and associated complications of juvenile- and adult-onset dermatomyositis (DM) differ significantly. The pathological hallmarks of DM are similar between juvenile dermatomyositis (JDM) and adult DM, including skin rashes and proximal muscle weakness; however, the prevalence and implication of associated autoantibodies varies, depending on age of onset.

Myositis specific antibodies (MSA) have been used as a prognostic tool to aid management of disease in both adult DM and JDM [1]. In JDM, a prevalent MSA is anti-TIF1γ, and is the most common MSA in Caucasian patients. Although the clinical and pathological features of anti-TIF1γ subtype are significantly heterogeneous [2, 3], this MSA has been well-known to be associated with malignancy in adult DM [4]. More specifically, we have previously shown that adult DM patients with cancer have significantly higher frequency and serological level of anti-TIF1γ-IgG2 isotype [4], which raises the question of whether there is also an association between anti-TIF1γ-IgG2 isotype and cancer in JDM. To explore this, we investigated all anti-TIF1γ isotypes and their associations with clinical manifestations in JDM.

We conducted a retrospective study of 31 patients to evaluate clinical features of anti-TIF1γ-positive patients from diagnosis to the most recent clinical visits (Supplementary Table S1. Available at Rheumatology online). The median duration of follow-up was 6.6 years (min 1.0 – max 20.6 years).

This cohort included 20 patients from French healthcare centres and 11 patients from the UK healthcare centres. Serum was collected near time of diagnosis or flare. Serum samples were first tested for anti-TIF1γ using either commercial Myositis Profile 4 EUROLINE immunoblot (EUROIMMUN AG, Lübeck, Germany) or immunoprecipitation. Within those with anti-TIF1γ auto-antibodies, anti-TIF1γ isotypes including IgG1, IgG2, IgG3 and IgG4 were measured using a multiplex ALBIA assay developed by Aussy et al. [5]. The median duration from diagnosis date to sample date was 10.3 months (IQR: 1.2 – 9.6).

Out of 31 children, 54.8% (17) were Caucasian, followed by North-African (Maghreb) (25.8%, n=7), and other minority groups. Male to female ratio was 14/17. Average age at diagnosis was 6.8 ± 3.3 years. All 31 patients had IgG1 isotype, and 14/31 had more than one isotype of anti-TIF1-γ. There was no mutual exclusion between 4 isotypes as various combinations of isotypes were found (Figure 1A).

Although the IgG2 isotype of anti-TIF1γ has been shown to be a biomarker for malignancy and mortality in adult DM, there was no report of malignancy in this paediatric cohort (Table S1). In our JDM cohort, the rate of IgG2-positive was 25.8% (8/31). We did not observe any difference in clinical presentation or outcome between IgG2-positive versus IgG2-negative patients.

Interestingly, there was a significant difference regarding anti-TIF1γ-IgG2 prevalence between ethnic groups (Kruskal Wallis’s test, p = 0.01, Supplementary Figure S1. Available at Rheumatology online). Specifically, although Caucasian patients were the majority (17/31, 54.8%) of this cohort, only 1 out of 8 (12.5%) IgG2-positive cases was Caucasian, which made the IgG2 prevalence significantly different from non-Caucasian population (Fisher’s exact test, p = 0.01)(Figure 1B). Notably, 4/8 IgG2-positive patients (50%) were found in North-African (Maghreb) population, making up 44.4% (4/9) of this ethnic group (Supplementary Figure S1).
We also observed that anti-TIF1γ isotypes can change over time. Specifically, of 6 patients tested for anti-TIF1γ isotypes at a second time point, 4 cases had changes in serological levels of anti-TIF1γ isotypes: 2 had lower titer levels, 1 lost positive status for IgG2 and IgG3, and 1 gained positive status for IgG4. Average time duration between the first and second sample time-points was 18.7 ± 13.4 months. Further investigation in larger cohorts is needed to clarify whether the changes in isotype titer are age-dependent or correlated to treatment response.

Two French patients in this JDM cohort died from persistently severe JDM which led to multi-organ failure despite being treated with corticosteroids, methotrexate, mycophenolate mofetil, rituximab and plasma exchange. Both patients were positive for IgG4 but negative for IgG2. Based on the analysis in the French cohort (as IgG4 was not detected in UK cohort), IgG4-positive patients might be more likely to have severe onset (Fisher’s exact test, p = 0.03)(Supplementary Figure S2. Available at Rheumatology online). Severity was defined according to previous consensus [6] by: i) admission to intensive care unit (ICU), and/or the presence of ii) skin ulcerations and/or iii) severe muscle involvement, defined by CMAS < 15 or MMT < 30, and/or iv) a severe organ involvement (e.g. cardiovascular, pulmonary or gastrointestinal involvement, dysphonia or dysphagia) within the first month of diagnosis. Larger sample sizes are required to confirm a potential association of severe JDM onset with anti-TIF1γ-IgG4 isotype and the potential impact on disease management, if this association is confirmed.

In conclusion, our study shows the distribution and fluctuation of anti-TIF1γ isotypes in JDM patients. Our data indicated that there may be a relationship between anti-TIF1γ IgG2 isotype and ethnicity. Importantly, although IgG2 is a biomarker for cancer in adult DM, it is not associated with severe onset or manifestations such as mortality or malignancy in JDM patients, which is consistent with previous reports [7,8].
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Contributorship
BBM, FJ, BD, NC, CG, CB, PQ, AB, IM, NF, KOB, DC LRW and ST contributed to the acquisition of data. ST ran the MSA analysis for UK cases. HDN conducted analysis and prepared the manuscript. LRW OB BBM conceptualised and designed the study, and critically reviewed the manuscript. All authors reviewed, edited, and commented on the manuscript. All authors approved the final revised manuscript.

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Competing interests
Lucy R Wedderburn declares consultancy fees paid by Pfizer to UCL for an unrelated project. Olivier Boyer declares consultancy fees paid by Argenx, BMS, CSL Behring, Egle Tx, OGD2, and UCB. Olivier Boyer also declares research grant support from Argenx and UCB. Other authors declare no competing interests.

Data availability
Data on the cohorts’ studies can be applied to through the corresponding author (LRW).

Ethics
The UK cohort study was fully approved by Yorkshire REC, MREC number 1/3/22, and IRAS number-229746. The French cohort study was approved by the institutional review board of Rouen University Hospital (ref NO. E2021-33). All patients provided full informed consent to participate.

Figure Legends
Figure 1 Detection of anti-TIF1γ auto-antibodies and demographic association in patients with JDM. Anti-TIF1γ auto-antibodies were measured by lineblot or immunoprecipitation. Anti-TIF1γ isotypes including IgG1, IgG2, IgG3 and IgG4 were measured using the multiplex ALBIA assay in both cohorts. A) Diverse combination of anti-TIF1γ isotypes detected in JDM patients from French and UK cohorts. B) Anti-TIF1γ IgG2 positive patients were analysed according to ethnicity: anti-TIF1γ IgG2 is more prevalent in non-Caucasian patients.

Supplementary Figures
Supplementary Figure S1. Prevalence of anti-TIF1γ IgG2 isotype in different ethnic groups.

Supplementary Figure S2. IgG4 is more prevalent in French JDM patients with severe onset.
References


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Figure 1

A

B

Fisher's exact test, \( p = 0.01 \)
No trend towards increased rates of malignancy, MACE or IBD over time  

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Adapted from Novartis Data on File. 2021.
Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children, and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active anklyosing spondylitis in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate; weight < 50 kg, recommended dose is 75 mg. However, 150 mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. Hydroalcoholic suspensions Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. Contraindications: Hypersensitivity to the active substance or excipients. Clinically important, serious infection or inflammation. Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur and do not continue treatment before consulting Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies. Should not be administered to patients with active tuberculosis (TB) infection therapy before starting Cosentyx in patients with latent TB. Inflammatory bowel disease (including Crohn’s disease and ulcerative colitis). New or exacerbation of pre-existing inflammatory bowel disease, secukinumab should be used with caution and appropriate medical management should be initiated. Hypersensitivity reactions: Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. Necrotic ulcerations: Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations with Cosentyx; inactivated or non-live vaccinations may be given. Patients should receive all age appropriate immunisations with Cosentyx; inactivated or non-live vaccinations may be given, except MMR. Interactions: No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study.