

Targeting IL-6 in treatment-resistant Blau syndrome: clinical and laboratory improvement following tocilizumab

Dear Editors,

Blau Syndrome and early-onset sarcoidosis represent two aspects of the same hereditary juvenile-onset systemic granulomatosis especially involving the eye with vision-threatening complications, the skin and the joints with articular deformities (1). There are no standardised guidelines for its management and treatment remains challenging (2). Anti-tumour necrosis factor (TNF) and anti-interleukin (IL)-1 agents have been used with inconsistent outcomes, with some patients exhibiting resistance to one class or the other (3-8). Therefore, identifying alternative therapeutic options is essential, particularly for patients failing to respond to available treatments.

We report the case of a 44-year-old woman carrying the *NOD2* Arg334Gln (R334Q) mutation, who presented with severe and longstanding disease. She had shown no clinical response to anti-TNF agents (adalimumab and etanercept) and IL-1 inhibition (canakinumab 300 mg/months).

Clinically, she displayed marked joint involvement with camptodactyly and granulomatous swelling predominantly affecting the hands and wrists. Figure 1 illustrates the joint deformities observed in the patient's hands. The patient was negative for rheumatoid factor and anti-cyclic citrullinated peptide antibodies; ultrasonography revealed lesions consistent with granulomatous synovitis. Ocular examination revealed significant bilateral band keratopathy, more pronounced in the right eye, alongside additional signs of previous inflammation, including sequelae of severe bilateral panuveitis and multifocal choroiditis, with presence of ghost vessels, chorioretinal scars at fundus examination.

At the time of assessment, the eyes showed signs of previous severe disease; however, there was no evidence of active ocular or cutaneous disease. Conversely, the patient presented inflammatory joint pain, consisting of the only reason requiring the chronic glucocorticoids use. Indeed, none of the previous treatments achieved adequate disease control to allow prednisone tapering below 7.5 mg/day. Given the refractoriness of joint involvement to prior biotechnological therapies and the need for a rapid steroid tapering, treatment with the anti-IL-6 receptor monoclonal antibody tocilizumab was initiated at a dose of 162 mg/week subcutaneously, with the primary aim of controlling joint pain and thereby enabling reduction of glucocorticoid dosage.

Articular symptoms began improving by the second month of therapy and continued to do so through month six and twelve,

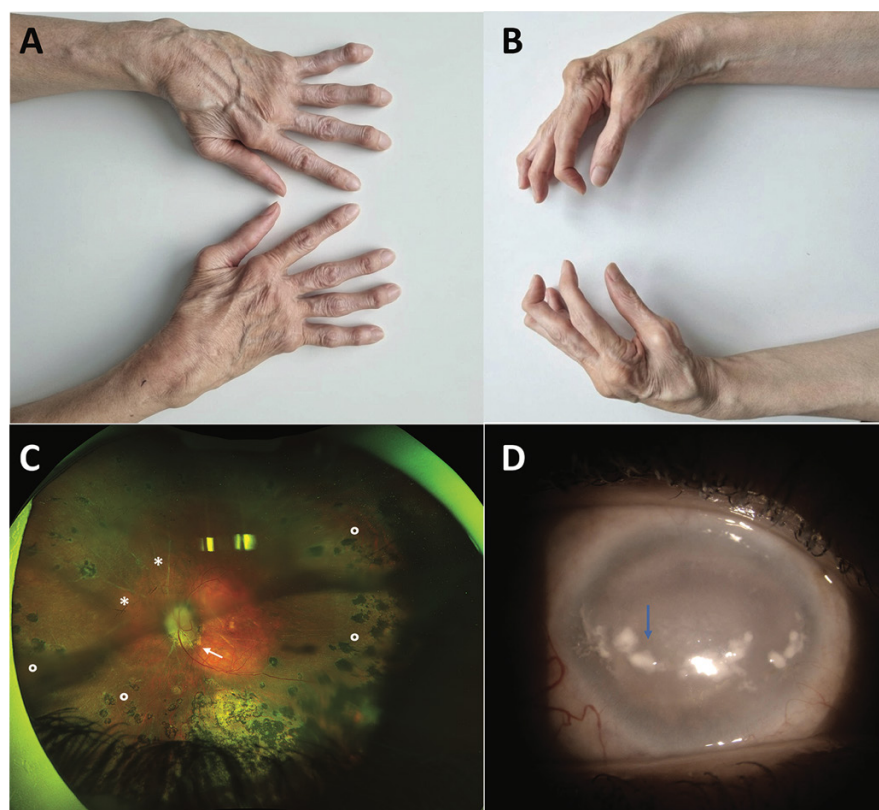


Fig. 1. Major clinical features observed in the enrolled patient affected by Blau syndrome.

Dorsal (panel A) and lateral (panel B) views of the hands, characterised by ulnar deviation of the fingers, joint subluxation, and impaired extension of the phalanges, consistent with acquired camptodactyly. This limitation in joint mobility prevents the attainment of a neutral anatomical position, resulting in a claw-like posture of the fingers. There is also significant involvement of the radiocarpal joints, characterised by progression toward carpal ankylosis. Panels C and D refer to the severe ocular involvement occurred in this patient. Fundus photography (panel C) of the left eye shows sequelae of severe panuveitis and multifocal choroiditis, including ghost vessels, more prominent nasally to the optic disc (*), as well as chorioretinal atrophic lesions in the mid and far periphery (°). The optic disc appears elevated with blurred margins and shows a few juxtapapillary chorioretinal scars (arrow). Panel D shows the right eye, which, following severe recurrent panuveitis and multiple surgical interventions, has developed phthisis bulbi associated with corneal decompensation and band keratopathy (blue arrow).

reaching a health assessment questionnaire score of 0.125. The joints patient global assessment decreased from 80/100 to 25/100. The number of tender joints decreased from 8 to 0, while swollen joints decreased from 2 to 0. Ocular involvement, which was already severely compromised at baseline, remained stable with no inflammatory exacerbations during follow-up.

Inflammatory markers normalised: CRP decreased from 14 mg/L to 0.4 mg/L, and LDH remained stable ranging between 138 and 144 mg/dl. Concurrently, anaemia resolved.

Importantly, prednisone was successfully tapered from a long-standing regimen of by 10 mg/day to 5 mg/day alternating every other day with 2.5 mg/day. This was particularly notable, as lower steroid doses had not previously been achievable, without triggering joint inflammation.

This case provides evidence of the tocilizumab effectiveness in Blau syndrome over a 12-month follow-up, thereby enriching the current literature, based solely on a single case treated for three months and

followed for five months (8). Despite the substantial pre-existing organ damage limiting the overall potential for clinical recovery, this case demonstrates that tocilizumab may offer meaningful symptomatic improvement and inflammation control in patients with *NOD2*-related disease refractory to both anti-TNF and anti-IL-1 therapies. In particular, the stabilisation and partial recovery observed highlight the therapeutic potential of IL-6 blockade.

Tocilizumab represents a promising addition to the therapeutic armamentarium for refractory cases of *NOD2*-associated disease. Future studies should evaluate its efficacy in patients with earlier-stage disease or less advanced structural damage, where the therapeutic window may be wider.

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