Letters to the Editor

Successful treatment of refractory adult-onset Still's disease with anti-CD20 monoclonal antibody

Sirs,

Adult-onset Still's disease (AoSD) is a rare systemic inflammatory disorder of unknown etiology typically presenting with high-spiking fever, a characteristic evanescent, salmon-pink, cutaneous rash and arthritis affecting both small and large joints (1). Pathogenesis is not completely understood. It has been suggested that environmental factors, including viral infections, may trigger the phenotypic expression of the disease in the setting of a specific genetic background (2). Moreover, immune dysregulation favouring a T helper (Th) 1 over Th2 response has been implicated in the pathogenesis. Indeed, Th1-type cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8 and IL-18, predominate in peripheral blood and tissue samples of patients with active untreated disease (1). In addition, IL-1 appears to play an important pathogenic role in disease manifestations, by enhancing circulating neutrophils, inducing fever and up-regulating ferritin levels (3). A potential pathogenic involvement of B cells is suggested by histological and immunohistochemical findings of lymph node biopsy of patients with AoSD, although their role remains to be elucidated (4). It has been established that, besides autoantibody production, B cells act as antigen-presenting cells activating T cells. Moreover, their role as cytokine producing cells has been recently highlighted (5). In this setting, descriptions of non-Hodgkin's lymphoma and Richter's syndrome developed in AoSD patients may further sustain a B cell involvement in the disease pathogenesis (6-8).

Increasing awareness of the pathogenic role of such cytokines has driven the use of novel anti-cytokine drugs in the treatment of corticosteroid (CS) and traditional immunosuppressive agent resistant-disease. In recent years, TNF-α inhibitors, anti-IL-6 receptor monoclonal antibody and IL-1 receptor antagonist, have been successfully employed in otherwise treatment-resistant cases (1). However, AoSD cases refractory to biologic therapies have been reported (9).

Here we describe a 59-year-old Caucasian man referred with a history of AoSD diagnosed in 1999. Disease was characterized by spiking, intermittent, fever (maximum 39°C), sore throat, asymmetrical arthritis and hepatosplenomegaly. Laboratory tests showed leukocytosis and abnormal liver enzymes. Rheumatoid factor and antinuclear antibodies were normal. Infective, neoplastic and connective tissue diseases were excluded and AoSD was diagnosed according to the presence of three major and four minor Yamacughi classification criteria (10). In 2001, methotrexate (MTX) was introduced to avoid chronic use of high doses of CS. Despite adequate treatment, disease remained active with recurrent febrile episodes, large joint inflammatory involvement, persistent leukocytosis and high ferritin and CRP levels. Use of infliximab 5 mg/kg in combination with MTX was ineffective. Subsequent introduction of etanercept, 50 mg weekly in combination with MTX, resulted in an only transient improvement of disease activity. The drug was discontinued after 18 months because of an adverse event (*Streptococcus faecium* pneumonitis). Disease relapse rapidly occurred after stopping TNF-α blockade and high CS doses needed to control inflammation. Serum ferritin levels raised to 5492 mg/dl and CRP to 10 mg/dl. Since disease proved refractory to traditional immunosuppressive and anti-TNF-α agents, anakinra administration was proposed, but patient refused daily subcutaneous injections. Anti-CD20 chimeric antibody (rituximab) was therefore considered as therapeutic option. The introduction of rituximab 1 gram (two infusions at 2-week interval) in combination with MTX induced progressive fever disappearance and polyarthritis regression. Immunoglobulins level before first infusion resulted: IgG=2490 mg/dl (normal range 650-1600 mg/dl), IgA=440 mg/dl (40-350 mg/dl) and IgM=113 mg/dl (50-300 mg/dl). Readministration of a second and a third cycle at 6 months interval was well tolerated. Prednisone was slowly tapered from 50 to 5 mg/day. Laboratory findings showed a decrease of leukocyte count (from 18.000/mmc to 8.350/mmc) and ferritin levels (from 5492 mg/dl to 735 mg/dl). Immunoglobulins level after the third infusion resulted within the normal range (IgG=1671 mg/dl; IgA=343 mg/dl; IgM=72 mg/dl).

To our knowledge, this is the third report of successful treatment of AoSD with rituximab since only other two cases of TNF-α-inhibitor resistant AoSD successfully treated with rituximab have been recently described by Ahmadi-Simab (11). It is to note that anti-CD20 treatment achieved a more delayed laboratory response with respect to the effects obtained with therapies directly targeting pro-inflammatory cytokines. Indeed, a normalization of laboratory parameters, including leukocytosis and CRP levels, was reported within a week after first tocilizumab infusion (12) with complete clinical and laboratory response after seven infusions (13). Similar rapid and sustained response, as shown by ultrasonographic findings of inflamed joints, has been described in AoSD patients following anakinra administration (14). These differences may probably reflect a different pathogenetic role of B cells in disease manifestations. In this setting, it is intriguing to note that our patient presented polyclonal hypergammaglobulinaemia with elevated IgG and IgA levels. Hypergammaglobulinemia is a non specific laboratory parameter reported in up to 69% of AoSD patients (15) and cannot be considered a marker of disease activity. However, if polyclonal hypergammaglobulinaemia may represent a potential prognostic factor to predict treatment response to rituximab is a hypothesis that needs to be confirmed by additional studies.

In conclusion, the present report suggests that rituximab may be considered an alternative treatment in some refractory AoSD cases (16). However, larger series of patients are required to confirm this hypothesis and to determine optimal length of treatment course.

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