The effect of tocilizumab on the uptake of $^{18}$FDG-PET imaging in patients with adult-onset Still’s disease

SIR, Adult-onset Still’s disease (AOSD) is a multisystemic inflammatory disorder of unknown cause where the clinical and laboratory manifestations appear to be mediated by IL-6.

It is characterized by daily spiking fever rash leucocytosis and musculoskeletal manifestations such as myalgias and arthritis [1]. Various treatments have been used in this disease without conclusive results. Tocilizumab is a humanized anti-IL-6 receptor antibody that is being introduced as a novel anti-rheumatic drug [2–4]. There is no gold standard for the image assessment of AOSD since the disease has articular and extra-articular features. $^{18}$FDG-PET–CT (PET–CT) is a modern and useful tool to evaluate articular and extra-articular synovitis (present in tendon sheaths) not juxta-articular [5]. We present two patients with AOSD who received three infusions of tocilizumab (8 mg/body weight) and had PET–CT performed for diagnostic purposes. PET–CT results are presented in Fig. 1A and B and semi-quantification of involved areas by standard uptake values (SUVs) is included in the text.

Patient 1 was a 72-year-old male with classical symptoms of AOSD with fever, anaemia and severe myalgias [Hb 8.2 g/l; WBC 18 000 mm$^3$; CRP 65 mg/dl; ESR 113 mm in the first hour; aldolase 17.5 Ul (normal range 7.0 Ul), approximately two and half times over the normal value; and ferritin 2833 ng/ml, upper limit of normal range 290 ng/ml for the age]. Patient 2 was a 56-year-old female with fever, severe arthralgias and anaemia (Hb 9.0 g/l, WBC 14 000 mm$^3$; CRP 78 mg/dl, ESR 98 mm in the first hour and ferritin 1532 ng/ml, upper limit of normal 280 ng/ml for the corresponding age). Both patients were on steroids when anti-IL-6 was started and when the initial PET–CT was performed they had already been on 20 mg of prednisone for ~6 weeks.

Patient 1 had abnormal uptake in the spleen (SUV = 3.6) and bone marrow (SUV = 4.7) (Fig. 1) and Patient 2 showed diffuse $^{18}$FDG uptake on quadriceps muscle bilaterally (SUV = 1.2) and a small uptake on the iliac bone (SUV = 3.6) (Fig. 2).

Both scans returned to normal pattern of distribution after treatment and so did the laboratory values. SUVs after treatment were, respectively, for Patient 1: spleen 2.0 and bone marrow 2.3; for Patient 2: muscle of the thighs 0.5 and iliac bone 1.2, indistinguishable from adjacent normal tissues.

Tocilizumab has been shown to be helpful in children with severe systemic-onset juvenile idiopathic arthritis but reports are also appearing showing good clinical responses in patients with AOSD [6–8]. The marked and rapid reduction of the uptake of $^{18}$FDG in our patients points to the possibility that PET–CT, together with other clinical and laboratory features, maybe a helpful tool in the follow-up of patients with AOSD in cases where clinical and laboratory parameters are not sufficient to document remission.

Finally, while the responses to tocilizumab indicate an important role for IL-6 in the pathogenesis of AOSD, significant levels of other cytokines have been described in the sera and tissues of such patients, and in fact some do...
show clinical response after the use of anti-TNF blocking agents [9–11].

**Rheumatology key message**
- In AOSD, tocilizumab induces a marked reduction on uptake of 18FDG.

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**References**


**Fig. 2** Increased uptake of 18FDG on quadriceps muscles before and after decreased tocilizumab.
Severe aplastic anaemia following leflunomide therapy

Sr, Aplastic anaemia represents a rare acquired disorder of haematopoiesis, which, in its severe form, is a life-threatening disease with high mortality rates. Often, the aetiology remains unknown; although, in some cases it can be attributed to myelotoxic drugs or viral infections. Here, we present the first clinical report of a patient with RA who developed irreversible severe aplastic anaemia (SAA) after treatment with LEF.

A 32-year-old female patient was diagnosed with RA in October 2007. Immunosuppressive therapy was started with LEF 20 mg/day and continued for 30 days. Prior to initiating treatment, her blood analyses revealed haemoglobin concentration, leucocyte count and platelet counts within normal laboratory range. Shortly after the initiation of treatment, her arthritis symptoms improved markedly. One month after the initiation of treatment, the patient developed fatigue, fever and extensive purpurae and ecchymoses. Peripheral blood analyses revealed the following values, consistent with pancytopenia: haemoglobin concentration, 8.2 g/dl; granulocytes, 0.2 × 10^9/l; platelets, 12 × 10^9/l and reticulocyte count, 0.4%. Bone marrow cytology and histopathology showed hypoplasia of haematopoietic lines without evidence of blasts or dysplasia. Bone marrow cytogenetic analyses disclosed a normal karyotype. The patient had a history of neither recent viral infection nor medication exposure other than LEF. Therefore, our diagnostic interpretation of the integrated findings was SAA, secondary to LEF exposure. At this point, LEF was discontinued and treatment with cholesterolamine started. Yet, there was progressive decline in circulating leucocyte, erythrocyte and platelet counts. The patient required several weekly transfusions of red blood cells and platelets. The clinical course was complicated by an abscess in the left mandible. Cultures of the lesion grew Actinomyces and Proteus mirabilis. Furthermore, a CT scan of the chest revealed bilateral pulmonary infiltrates consistent with invasive aspergillosis. Despite treatment with antibiotics and anti-mycotics, both the left mandibular abscess and the pulmonary aspergillosis did not demonstrate any significant clinical improvement.

In this critical situation with ongoing severe aplasia over months, the decision was taken to perform allogeneic bone marrow stem cell transplantation (SCT) with an HLA-identical sibling donor in July 2008. Following engraftment, there was gradual improvement of the pulmonary lesions. Development of severe graft vs host disease (GvHD) of skin and intestine required application of high dosage steroids and a switch of calcineurine inhibitor treatment to tacrolimus. However, the recovery period from SCT was complicated by several exacerbations of the pulmonary aspergillosis, requiring atypical lung resection, which was successfully performed in April 2009. At the time of this report—12 months from SCT—the patient has normalized peripheral blood parameters and complete donor chimerism. She is currently without any signs of infectious disease or graft vs host disease. Immunosuppression has been reduced and RA has not reappeared.

Acquired aplastic anaemia can be considered as an autoimmune disorder characterized by cytotoxic T-cell-mediated destruction of bone marrow haematopoietic cells [1]. However, in most cases, the trigger of this aberrant autoimmune reaction remains unclear. In some patients, the immune response can be linked to a viral infection or to drug or chemical exposure [2]. LEF is a broadly prescribed DMARD that was approved by the Food and Drug Administration (FDA) for the treatment of RA in 1998 [3]. Single case reports indicate that LEF may be associated with the occurrence of haematological toxicity [4–7]. Most patients were concomitantly treated with other DMARDs, especially MTX [8]. Data from the European Medicines Agency (EMEA) revealed that concomitant treatment with LEF and MTX presented an increased estimated incidence of pancytopenia, which resulted in safety restrictions in March 2001 [9]. A drug safety alert update on LEF, including a warning regarding immunosuppression potential and bone marrow suppression, was posted by the FDA in November 2003. In most reported cases, the pancytopenia was transient and self-limiting when LEF was stopped.

An active metabolite of LEF is an immunomodulator that impairs the proliferation of activated T lymphocytes. In actively dividing cells, the metabolite halts de novo biosynthesis of pyrimidine nucleotides by inhibiting the enzyme dihydro-orotate dehydrogenase (DHODH). Other cells, in general, have low levels of DHODH activity and may utilize pyrimidine nucleotides from the salvage pathway to survive [10]. In the context of possible aberrant T-cell regulation in the pathogenesis of acquired aplastic anaemia, these contradictory mechanisms suggest that the LEF-mediated myelosuppression could involve a T-cell-independent mechanism. Direct injury of both proliferating and quiescent haematopoietic cells may impair DNA replication and trigger apoptosis. Genetic or epigenetic alterations could explain the rarity of the disease.

To our knowledge, this is the first case report of irreversible SAA, following treatment with LEF, which required allogenic SCT. This case highlights the need for frequent blood count monitoring during treatment with LEF. In these patients, clinicians should consider the rare incidence of SAA when there is agranulocytosis or pancytopenia.