Spectacular efficiency of Tocilizumab in a refractory systemic form of adult-onset Still's disease: a case report

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ABSTRACT

INTRODUCTION

Adult-onset still's disease (AOSD) is a rare systemic inflammatory disorder. Its treatment is not based on controlled study, but on case based experiences. It combines corticosteroïds and Méthotrexate (MTX).

Until 2016, the literature reported only about fifty patients with refractory AOSD treated with anti-IL-6 (Tocilizumab). We report a new observation.

PATIENTS AND METHODS

A previously healthy 20-year-old male patient, was referred to our hospital for persistent high fever with a deterioration of the general status, evanescent skin rash, sore throat, hépato splenomegaly, arthritis ,arthromyalgia.
Laboratory tests revealed marqued inflammation, hyperferritinemia , striking neutrophilic leukocytosis and abnormal liver function tests. The immunological test was clear.

The patient was diagnosed as AOSD after infection, malignancy, hematologic disorders, and other autoimmune diseases were excluded. Pulsed methylprednisolone therapy was initially administrated, relayed with oral prednisone, but because of steroid-resistance, no remarkable results were noted.

MTX with effective dose, and infusions of intravenous immunoglobulins, were unable to ameliorate the patient's
conditions.
The symptomatology was getting worse,then, we add Tocilizumab (TCZ) intravenously.

FOLLOW UP

Impressive improvements were obtained allowing a sustained remission.

LEARNING POINTS :

- **Efficiency of Tocilizumab in a refractory systemic form of AOSD.**
- **Tocilizumab could offer an alternative to Anakinra in case of systemic refractory form**

INTRODUCTION :

AOSD is a rare inflammatory disease, the incidence is estimated at 0.16 / 100 000 inhabitants [1].

It is characterized by a clinical triad (fever, arthralgia or arthritis and rash) and biologically by an inflammatory syndrome with a decrease of the glycosylated fraction of ferritin. The diagnosis of AOSD is based on classification criteria of Yamagushi and Fautrel [2], however, it remains a diagnosis of exclusion. The first-line treatment is based on steroids and MTX.

The therapeutic management of AOSD has been revolutionized thanks to the new targeted therapies, such as antiTNFα, anti IL-6 and anti IL-1 (Anakinra), which have been used successfully in conventional treatment-resistant cases [2].

TCZ has been reported to be more effective in articular forms, while Anakinra has shown better results in systemic forms [2]. We report an observation, where the TCZ has been used successfully in a severe and refractory systemic form of AOSD.

OBSERVATION

A previously healthy 20-year-old male patient, was referred to us for persistent high fever, deterioration of the general status, evanescent skin rash, odynophagia, pharyngitis , hépatomegaly, splenomegaly , arthritis of the right ankle ,arthromyalgia.
Laboratory tests revealed marqued inflammation (ESR :45 mm/h , CRP : 96 mg/L), hyperferritinemia>2000 ng/mL , striking neutrophilic leukocytosis (390000/ uL) and abnormal liver function tests (AST : 2x upper limit of normal (ULN), ALT : 4xULN, GGT : 6xULN et ALP : 3xULN).The immunological test was clear.
After infection, malignancy, hematologic disorders, and other autoimmune diseases were excluded, the diagnosis of AOSD in its systemic form was established since the patient fulfilled all the Yamagushi and Fautrel criteria exept the glycosylated fraction of ferritin.

The patient was treated with boluses of methylprednisolone 1g / day for 3 days, with a clear clinical improvement. We relayed with oral prednisone 1 mg / kg / day , then, we increased to 2mg / kg / day because of steroid-resistance , but no remarkable results were noted.

So we added MTX (20 mg / week) and intravenous immunoglobulins infusions (2 g / kg) .
The symptomatology was getting worse, with appearance of consciousness disorders, then, we decided to add TCZ intravenously (8 mg / kg / month).

We noticed an improvement of the general status, decrease of the fever as well as arthromyalgia. The second infusion allowed to obtain a remission with total apyrexia, disappearance of the consciousness disorders and the rest of the symptomatology, with decrease of the inflammatory syndrome, and correction of all the biological test. Currently, after 7 infusions of TCZ, the patient still in complete remission. MTX was maintained at 20 mg / week, with steroids decreasing to 10 mg / day.

DISCUSSION

The first-line treatment for AOSD is steroids and MTX, with 65% success for steroids alone and 40-70% for MTX [3].
In refractory AOSD forms, biotherapies have been shown to be effective, particularly Anakinra, in systemic forms and TCZ in articular forms [2].

According to that, the adequate biotherapy for our patient, would have been the Anakinra, but in front of the non availability of this drug, we had to choose TCZ.
This choice was supported by the results of the series of cases found in the literature.
It should be noted that very few studies are available, overall, until 2016, about fifty cases of refractory AOSD treated with TCZ have been reported.

The main retrospective serie, of Ortiz-Sanjuan 34 patients followed for refractory AOSD and treated with TCZ revealed disappearance of articular symptoms in 68% of patients, with a marked improvement in systemic signs, and normalization of biomarkers of inflammation [4].

As for the serie of Cipriani and al. (11 patients) th e TCZ allowed complete remission in 82% of patients. Also, the serie of Puéchal and al (14 patients), the success rate was 86% [4].

For our patient, after 2 infusions of TCZ, there was a spectacular improvement in the general condition, with disappearance of all symptoms and correction of all biological tests.
In addition to steroids withdrawal, TCZ has been able to achieve sustained remission.

The length of treatment with TCZ remains to be determined, its been indicated treatment ranging from 6 to 18 months[4].

CONCLUSION

Our observation provides an additional argument for the efficiency of Tocilizumab in AOSD refractory to first-line treatment.
Its has been shown to be effective in the articular and the systemic form of AOSD, which could offer an alternative to Anakinra.
This treatment appears to be promising in case of refractory AOSD, but larger scale studies are necessary.

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