TOCILIZUMAB FOR DIFFICULT-TO-TREAT IDIOPATHIC RETROPERITONEAL FIBROSIS. A PILOT TRIAL

Dr Augusto Vaglio, Dr Federica Maritati
Unit of Nephrology,
University Hospital of Parma,
Via Gramsci 14,
43126 Parma (Italy)

Phone: +39 0521 702454; 702013
email: augusto.vaglio@virgilio.it

BACKGROUND

Idiopathic retroperitoneal fibrosis (IRF) is a rare autoimmune disease, hallmarked by a periaortic fibro-inflammatory tissue, which extends from the adventitia of the abdominal aorta and the iliac arteries into the surrounding retroperitoneum, often causing ureteral obstruction and acute kidney failure[1]. IRF usually responds to glucocorticoids, that induce rapid resolution of symptoms, normalization of acute-phase reactants, and mass shrinkage. However, 24% to 72% of patients experience a relapse, half of them repeatedly [2]. Steroids can be effective also in the treatment of relapsing disease, but a steroid-sparing treatment is necessary in order to avoid toxicity related to a prolonged cumulative exposure to steroids[3]. A valid alternative is also necessary for those patients who have refractory disease or contraindications to glucocorticoid therapy; contraindications to glucocorticoids include steroid-induced psychosis, severe osteoporosis with vertebral collapses, uncontrolled diabetes and/or dyslipidemia, which may be frequent in the population of patients with IRF, whose mean age at disease onset is 55-60years and whose cardiovascular risk profile is often unfavourable.

Interleukin-6 receptor (IL-6R) blockade with tocilizumab (TCZ) has proven effective for many autoimmune or inflammatory diseases, such as rheumatoid arthritis, juvenile idiopathic arthritis, and large-vessel vasculitides. IL-6 induces activation and differentiation of B cells, differentiation of CD4+ cells into IL-17–producing T helper cells and activation of CD8+ cells. Finally, IL-6 induces fibrosis through different mechanisms, including fibroblast to-myofibroblast differentiation, collagen deposition and the interactions with metalloproteinase activity. We have recently described the efficacy of TCZ in two patients with IRF, and also reported that IL-6 is intensely expressed in IRF biopsies by different cell types and that its serum levels are also increased[4]. In the above two patients, TCZ was successfully used alone or in combination with low doses of prednisone.

AIMS OF THE STUDY

In this prospective, open-label, single centre trial we will analyse the efficacy and safety of TCZ in a series of 12 patients with IRF who either experienced frequent relapses under adequate immunosuppressive therapy or had a clearly refractory disease and/or contraindications to glucocorticoid therapy.

ELEGIBILITY CRITERIA

Inclusion criteria

- Clinically active IRF (either newly diagnosed or relapsing/refractory)
- Age 18-80 years
- Informed consent
- at least <u>one of the following</u>:

a) Refractory disease: disease unresponsive to standard glucocorticoid therapy (initial dose 1 mg/kg/d) +/- conventional immunosuppressants (MTX, MMF)
b) Previously reported serious adverse events related to the use of standard dose glucocorticoids, particularly neuropsychiatric effects, hypersensitivity reactions, uncontrolled diabetes, severe cardiovascular events
c) Common contraindications to standard-dose glucocorticoids: uncontrolled diabetes, severe hyperlipidemia, severe osteoporosis (e.g., with previous vertebral fractures), high-risk cardiovascular profile, severe obesity

Exclusion criteria

- chronic viral infections (HIV, HBC, HCV)
- documented contraindication to TCZ or others biologic agents
- pregnancy
- concurrent malignancies or malignant neoplasms that occurred during the 5 years prior to enrolment (with the exception of adequately treated non-melanoma skin cancers)
- secondary forms of retroperitoneal fibrosis
- stable and/or unstable angina or known, untreated, coronary artery disease.

In addition, latent tuberculosis has to be excluded by tuberculin skin testing and/or serum Quantiferon test and chest radiographs. In patients with latent tuberculosis, prophylaxis with isoniazid has to be initiated 4 weeks before the onset of TCZ and maintained for at least 9 months. Written informed consent will be requested and obtained from all patients before starting the treatment.

LABORATORY TESTS, IMAGING STUDIES AND DIAGNOSTIC BIOPSY

At study entry, the patients will undergo physical examination, routine laboratory tests including full blood counts, renal and thyroid function, CRP, ESR, IL6, serum protein electrophoresis, lipid profile and urinalysis. In addition, immunologic tests such as total immunoglobulins and IgG subclasses, ANA, anti-ENA, anti-dsDNA, and ANCA dosage will be performed. All patients will undergo testing for lymphocyte subpopulations before starting treatment. 5 ml of serum will be obtained (at months 0, 2, 4, 6, 9 and 12) and stored at -80°C for future studies on disease biomarkers.
The diagnosis of IRF has to be confirmed by contrast-enhanced CT or MRI. FDG-PET will also will be employed to assess disease activity. A laparoscopic or laparotomy biopsy will be performed only when a secondary form of retroperitoneal fibrosis is suspected.
In case of severe unilateral or bilateral hydronephrosis with acute kidney failure, patients will undergo ureteral decompression with conservative (stents or nephrostomy) or surgical (ureterolysis) procedures before starting the treatment. This choice will be left at the discretion of the treating clinician.

TREATMENT

Patients will receive a monthly TCZ dose of 8 mg/kg for six months; a follow-up period of at least an additional 6 months will follow. Where the treating clinician considers that patients can be safely treated also with low-dose glucocorticoids, prednisone can be prescribed at an initial maximum dose of 25 mg/day and then tapered within 4-6 weeks to a maintenance dose of 5 mg/day. In patients with refractory disease or in patients who experienced relapse during glucocorticoids or other immunosuppressive therapy (e.g., methotrexate), TCZ will be used as add-on therapy.

ASSESSMENT OF EFFICACY AND TREATMENT-RELATED TOXICITY

The assessment of treatment efficacy will be evaluated as the **rate of remission at months 6 and 12**. Remission will be defined as absence of disease-related symptoms (abdominal or lumbar pain, testicular pain, constipation, systemic symptoms), resolution or improvement of hydronephrosis (without indwelling stents), near-normalization (i.e. normalization or reduction to <30% of basal values) of erythrocyte sedimentation rate and C-reactive protein levels, as previously described [2].

Secondary outcomes will include the assessment of the percentage of reduction in IRF thickness at CT or MRI scans and the reduction of FDG uptake (measured as SUVmax) at PET-CT.

CT or MRI will be performed at month 0, 2, 6 and 12, and PET-CT at month 0,6 and 12.

Patients will be evaluated monthly during the treatment course and every 3 months after remission.

Adverse events and toxicity will be assessed at each scheduled visit by physical examination and routine exams. Eventual adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4 [5].

DATA COLLECTION AND STATISTICAL ANALYSIS

During each visit, patient's data will initially be recorded by hand by the investigator(s) on paper and then entered into an electronic data management file.

EXPECTED RESULTS AND FUTURE DIRECTIONS

This pilot trial should demonstrate/confirm the efficacy of TCZ for the treatment of IRF. We will design a long-term trial to evaluate which treatment schedule is better to maintain disease remission (e.g. serial TCZ administration), in order to have a staged remission-induction and remission-maintenance approach based on the use of TCZ.

REFERENCES

1. Vaglio, A., et al., *Retroperitoneal fibrosis.* Lancet, 2006. **367**(9506): p. 241-51.

2. Vaglio, A., et al., *Prednisone versus tamoxifen in patients with idiopathic retroperitoneal fibrosis: an open-label randomised controlled trial.* Lancet, 2011. **378**(9788): p. 338-46.

3. Alberici, F., et al., *Methotrexate plus prednisone in patients with relapsing idiopathic retroperitoneal fibrosis.* Ann Rheum Dis, 2013. **72**(9): p. 1584-6.

4. Vaglio, A., et al., *Interleukin-6 as an inflammatory mediator and target of therapy in chronic periaortitis.* Arthritis Rheum, 2013. **65**(9): p. 2469-75.

5. *CTCAE. NCICtcfaev. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-*