

## Tocilizumab in recent polymyalgia rheumatica: how can we manage the interleukin-6 blockage?

Thanks to Dr Moiseev *et al*<sup>1</sup> for their very interesting opinions on the treatment of polymyalgia rheumatica (PMR) with tocilizumab (TCZ). In the TENOR study,<sup>2</sup> for the first time, treatment other than glucocorticoid (GC) was able to control PMR. All patients received TCZ alone during 24 weeks. All parameters were improved: clinical symptoms, biological inflammation, patient's evaluation on disease activity, quality of life and imaging procedure.<sup>3</sup> This highlighted the role of interleukin-6 (IL-6) in the pathogenesis of the PMR and probably in giant cell arteritis. IL-6 was first described for its role in adaptive immunity but it also plays a fundamental role in innate immunity and regulates the acute-phase response raising the inflammatory aetiology of PMR.

In 2016, one of the new questions is the therapeutic strategy in PMR. Moiseev *et al* suggested TCZ agent as first-line therapy for PMR and asked about the side effects and cost-effectiveness of such therapy. Recent recommendation on PMR treatment<sup>4 5</sup> did not suggest IL-6 inhibition but pointed out the side effect of GCs and recommend lower dosage with rapid decrease to obtain 10 mg/day at week 8 and to add methotrexate if predictor of corticoreistance are present. All the recent data on TCZ suggest some modifications.<sup>6</sup>

In recent PMR, IL-6 inhibition should be considered in different cases: (1) for patients with associated comorbidities related to GC side effect (severe osteoporosis, diabetes), TCZ alone or in association with GC at lower doses following the TENOR protocol (ie, three infusions of TCZ and then a low dose of GC (0.15 mg/kg/day according to the PMR-activity score (AS))); (2) for patients with recent side effects (fracture), TCZ alone; (3) for patients with corticoredependence (inability to decrease GC) at week 8 and for GC dosage of more than 5 mg/day.

In long-lasting PMR, studies are needed to confirm that IL-6 inhibition has also a dramatic effect and to better define the level of response and the side effects in elderly patients with longer GC impregnation. However, in such patients, TCZ seems to be the major option in association with GC and a protocol of rapid decrease of GC dosage.

Side effects related to the inhibition of IL-6 should be closely monitored. They occur shortly after TCZ infusion and commonly include neutropenia, liver transaminases, serum lipid levels and alterations in cholesterol composition. Relationship with the dosage of TCZ is unknown but suggested. Moiseev *et al* suggested lower dosage of TCZ (4 mg/kg). In the TENOR study, where side effects were closely monitored, 59 infusions were administered, 52 at 8 mg/kg and 7 at 4 mg/kg, meaning 'only' 11% had a lower dosage. So, our data suggest close

monitoring and 8 mg/kg as the reference. These data need to be confirmed by future randomised trials and should also be considered with regards to the type of IL-6 inhibitors. Targeting the IL-6 or the cognate IL-6 receptor or selectively blocking IL-6 trans-signalling could have different effects and side effects.<sup>7</sup>

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