

## Editorial Title:

# The long-term use of Tocilizumab in Giant Cell Arteritis

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Fiona Coath, Chetan Mukhtyar

Autoimmune rheumatic diseases are known for their chronicity and relapsing course. The tunnel that is the duration of Giant Cell Arteritis (GCA) may however be finite, with light at the end of it. Stone et al have recently published the 12-month extension of their landmark clinical trial demonstrating the efficacy of the Interleukin-6 receptor inhibitor Tocilizumab.(1, 2) The role of interleukin-6 in GCA was first demonstrated in 1990.(3) This was put to practical use for inducing remission in refractory GCA in 2011.(4) Two randomized controlled trials have demonstrated the efficacy of sustaining remission up to 52 weeks (Table 1). Both studies used concomitant glucocorticoid therapy. In a proof-of-concept study, tocilizumab has been shown to induce remission as monotherapy in a smaller open labelled trial.(5) On the basis of these data, funding authorities have made the drug available for use in patients with relapsing and refractory disease (6).

Saito et al demonstrated that tocilizumab could induce remission without concomitant glucocorticoids.(5) Stone et al demonstrated that tocilizumab monotherapy after 26 weeks of prednisone can sustain remission in over half of individuals with GCA (Table 1). The open labelled extension has demonstrated that 24% of individuals can sustain remission without any further treatment for an additional year (Supplementary Table 1). Randomized controlled trials are the pinnacle of testing the efficacy of a new intervention, unadulterated by the artefactual influences of daily clinical practice. We therefore know with a high degree of certainty that of the 4 arms of their clinical trial, Stone et al have demonstrated that the strategy of giving tocilizumab 162 mg subcutaneously every week with a 26-week prednisone taper is superior at 52 and 104 weeks over prednisone therapy for 26 or 52 weeks. However, extrapolation beyond the clinical trial is often tricky.

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3 In reality the taper of glucocorticoid will take over 18 months, if not longer.(8-10) So it is difficult to  
4 infer the real gains made.  
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7 Cumulative glucocorticoid toxicity is of great concern in GCA. It is estimated around 85% of individuals  
8 with GCA will experience glucocorticoid related side effects.(11) The use of tocilizumab certainly  
9 appears to be 'steroid-sparing' to a magnitude of about 50%, but this does not appear to have resulted  
10 in a significant difference in adverse events. In Stone et al, individuals receiving tocilizumab suffered  
11 25.4 (95% CI 21.1-30.2) serious adverse events per 100 patient-years; those treated without  
12 tocilizumab suffered 23.2 (95% CI 17.0, 31.1) per 100 patient-years.(2) We know from long-term  
13 studies of ANCA associated vasculitis where the glucocorticoid burden is high, that infections  
14 contribute to early mortality and cardiovascular events contribute to long-term mortality.(12) The use  
15 of tocilizumab appears to have a similar infection risk in the open-label extension published by Stone  
16 et al.(2) Over a 14 year period, Andersen et al have shown GCA to have a standardized mortality ratio  
17 of 1.05 (95% CI 0.77-1.38), which is no different to the general population.(13) The occurrence of 4  
18 deaths in 100 patient-years (equivalent to 50 individuals treated over 2 years) with tocilizumab,  
19 compared with none who did not receive tocilizumab, should spark longer term vigilance.  
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23 In the pre-glucocorticoid era, Robertson observed the natural history of the disease and commented  
24 that "The disease often lasts up to a year; it seems to be self-limited and is rarely fatal".(14) The  
25 potential of the disease to do significant irreversible damage has spurred the trial and use of  
26 glucocorticoids.(15) But even then Birkhead et al commented "corticosteroids merely suppress the  
27 manifestations of temporal arteritis but do not actually alter the course of the disease...symptoms  
28 recurred after a varying period of treatment as the dose...was reduced below a critical value".(15) The  
29 side effect profile of glucocorticoids has led to the search for a better way to modify disease and  
30 reduce cumulative glucocorticoid exposure. For the most part this search has been low priority and  
31 not resulted in significant change in our practice. In their two papers, Stone et al have demonstrated  
32 encouraging truths -  
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- 35 1. A small proportion of individuals (about 10%) (Supplementary Table 1) need only 26-52 weeks of  
36 glucocorticoid treatment and identification of those individuals forms part of an urgent research  
37 agenda.  
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- 39 2. A further 15% can be put in long-term remission with tocilizumab for only 1 year. This will be a  
40 great relief to healthcare funders and patient groups alike.  
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- 42 3. Although the others will need longer-term tocilizumab, the 'steroid-sparing' is real and  
43 meaningful. The data at this stage do suggest that at 2 years, there isn't a benefit in terms of  
44 adverse event reduction, but this will undoubtedly change in the long-term. The real problems of  
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3 glucocorticoids are due to the long-term metabolic changes which result in greater mortality,  
4 morbidity, healthcare usage and quality of life. Tocilizumab can probably change all of that.  
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**Table 1: Randomized controlled trials of Tocilizumab**

Author	Primary endpoint	@time	Arms of trial	Result	P value
Villiger et al 2016 (7)	Complete remission of disease at a prednisolone dose of 0.1 mg/kg per day	Week 12	Tocilizumab 8 mg/kg iv 4 weekly + prednisolone	17/20 (p=0.03)	0.03
			Placebo + prednisolone	4/10	
Stone et al 2017 (1)	Sustained glucocorticoid free remission	Week 52	Tocilizumab 162 mg/kg/week + 26-week prednisone taper	56/100	<0.001
			Tocilizumab 162 mg/kg/2 weeks + 26-week prednisone taper	26/49	
			Placebo + 26-week prednisone taper	7/50	
			Placebo + 52-week prednisone taper	9/51	