Tocilizumab, an interleukin-6 inhibitor: a steroid sparing agent in giant cell arteritis

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Title Trial of tocilizumab in giant-cell arteritis

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Summary

The Giant Cell Arteritis Actemra (GiACTA) study, the largest randomised trial for this disease to date, involved 251 patients and describes the benefits of tocilizumab, an interleukin-6 inhibitor.[1] Patients were randomised to one of 4 groups, in a ratio of 2:1:1:1, to receive: subcutaneous tocilizumab 162 mg weekly (100 patients); or every 2 weeks (50 patients); or placebo (one arm of 50 patients and another of 51). In 3 arms of the study, all patients were subject to protocol defined prednisolone tapered over 26 weeks, such that prednisolone was discontinued by week 26 and replaced with placebo. In one of the placebo arms prednisolone taper was extended over 52 weeks, achieving a prednisolone dose of 7 mg at 26 weeks followed by reductions of 1 mg every month thereafter.[2] Prednisolone doses in a range of 20 to 60 mg were permitted at enrolment and tapering was based on that enrolment dose. When a dose below 20 mg was achieved, numbered blistered packs were provided to allow blinded steroid administration. The study was funded by Hoffmann-La Roche. Ten of the 16 listed authors disclosed conflicts of interest in relation to Roche.

Patients aged 50 years or older with newly diagnosed active giant cell arteritis (GCA) or relapsed GCA within 6 weeks of baseline were recruited. Active disease was defined by unequivocal clinical signs and symptoms attributable to GCA (new localised headache, scalp or temporal tenderness, vision loss attributed to ischaemia or otherwise unexplained mouth or jaw pain on mastication or typical polymyalgia rheumatica symptoms combined with imaging or biopsy evidence of vasculitis) with a raised erythrocyte sedimentation rate (ESR) (≥ 30 mm/h) and/or C-reactive protein (CRP) (≥ 1 mg/dL). The number of relapsed or refractory subjects was capped at 70% of recruits. The authors, appropriately, devised new diagnostic criteria for GCA such that modern imaging data could be included.[2] Concomitant methotrexate was permitted if started more than 6 weeks before enrolment. Notable exclusions were patients who had a history of diverticulitis, a prior episode of major infection or a prior malignancy. Patients had a mean age of 69 years.

The primary aim of the study was to demonstrate superiority of tocilizumab treatment, in terms of the proportion of patients achieving steroid free remission at 52 weeks, against placebo patients who tapered prednisolone over 26 weeks. A key secondary aim was to demonstrate the non-inferiority of tocilizumab versus placebo patients tapering over 52 weeks (non-inferiority margin of -22.5%). Tocilizumab may normalise CRP and ESR[3] without necessarily inducing disease remission thus, to minimise bias, a sensitivity analysis that excluded a need for normal CRP was done on these outcomes. To ensure blinding, all trial personnel were unaware of CRP levels. Efficacy was assessed by clinicians who managed the prednisolone taper. A laboratory assessor notified efficacy assessors of ESR values ≥ 30 mm/h, thus risking un-blinding in these patients. Disease flare was defined as a recurrence of clinical features of disease or an ESR ≥ 30 mm/h or the necessity for an increase in prednisolone dose. Remission was defined as an absence of flare and normalisation of CRP (≤ 1 mg/dL). Sustained remission was defined as remission from weeks 12 through 52 and adherence to prednisolone taper. Patients who flared, or could not adhere to prednisolone taper, switched to open-label prednisolone but continued tocilizumab or placebo as allocated at inception.

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Table 1 GiACTA study. Key data at 52 weeks

Allocation	Sustained remission	Actual cumulative prednisolone dose	GCA Flare	Escape prednisolone treatment	Withdrawal due to adverse effect	Serious infection
Tocilizumab weekly (n = 100)	56%	1862 mg	23%	23%	6%	7%
Tocilizumab every other week (n = 50)	53%	1862 mg	26%	33%	6%	4%
Placebo (steroid taper 26 weeks, n = 50)	14%	3296 mg	68%	74%	4%	4%
Placebo (steroid taper 52 weeks, n = 51)	18%	3818 mg	49%	55%	0%	12%

This study demonstrated that 162 mg of subcutaneous tocilizumab, given weekly or every 2 weeks, when combined with a 26-week prednisolone taper is superior to prednisolone taper alone over 26 or 52 weeks in terms of sustained steroid free remission, disease flare and cumulative steroid dose (see Table 1). Key efficacy data attained statistical significance ($p < 0.001$). Adverse effects were comparable though more patients withdrew from tocilizumab due to adverse effects than those on prednisolone alone. Neutropenia, a known adverse effect of tocilizumab, occurred in 4% of tocilizumab patients. Data on osteoporotic fractures were not reported but all enrolled patients were expected to receive calcium and vitamin D but use of bisphosphonates was left to the discretion of the treating physician.

Opinion

GCA, the most common form of vasculitis in older people, responds very well to corticosteroids. Between 51% and 72.5% of patients achieve permanent remission or can discontinue steroids after a median of 21.6 months.[4,5] In addition, 91% can reduce prednisolone to 5 mg per day after a median of 7.5 months (range 0.2 to 62 months).[5] Despite these impressive responses a substantial proportion of patients experience adverse effects. For example, around 35% of treated patients experience a vertebral or a femoral fracture,[4,5] bearing in mind that the population prevalence of vertebral fracture in women over 50 years is 14%[6] and that the incidence of vertebral fracture in women over 70 years is around 2% per annum.[7]

Clinicians offering steroid-sparing drugs tend to rely on methotrexate or azathioprine. Data for azathioprine are unconvincing but more convincing is the role of methotrexate.[8,9] A meta-analysis of randomised trials of methotrexate for GCA found that 63% of treated patients experienced a first relapse (including those with non-cranial symptoms) after 48 weeks of treatment compared with 80% of placebo treated patients (hazard ratio for methotrexate 0.65, confidence interval 0.44 to 0.98).[10] Fractures, a rate of 8%, occurred equally in methotrexate and placebo treated patients. Tumour necrosis factor-α inhibitors have not shown benefit for polymyalgia rheumatica or GCA but promising data for abatacept, an inhibitor of T cell activation via CTLA-4, using a drug withdrawal design, were published recently.[11]

The GiACTA study is a major international effort to find an alternative to steroids to treat this disease. The investigators should be congratulated, particularly as the study tackles key challenges which include diagnosis, defining the standard of care in relation to steroid taper, incorporating prednisolone blinding, defining endpoints including flare and remission, and preventing un-blinding where one of the mechanisms of action of the therapy tested is to suppress acute-phase proteins, which are key aspects of assessing disease.

Yet, important challenges remain. Diagnosis can be difficult despite new imaging techniques. Assessing disease activity or relapse is particularly challenging when relying on common symptoms such as visual disturbance, headache and shoulder pain in older people. Stone and colleagues excluded patients with a history of diverticulitis, presumably because patients treated with tocilizumab have a higher risk of gastrointestinal perforation, as do those on corticosteroids.[12] In addition, patients with a prior malignancy were excluded. The mean age of included patients was 69 years compared with 75 years in a large observational study.[9] These aspects may limit the generalisability of this study to routine practice. One key concern with the study design is the fact that laboratory assessors reported raised ESR ($\geq$ 30 mm/h) to efficacy assessors. This event is much more likely to occur in placebo treated patients, due to the effect of tocilizumab on acute-phase proteins,[3] thus risking un-blinding and bias towards attribution of clinical features to flare or active disease in placebo treated patients.

Cessation of steroids in around half of conventionally treated GCA patients may take 2 years. Observations over a longer time should provide greater insight into the benefits and risks of tocilizumab. The investigators set a high bar for response to treatment by depending on remission and complete cessation of prednisolone. Clinicians may regard a prednisolone dose below 5 mg daily acceptably safe and sufficiently good with any steroid sparing therapy.[13] However, the risk of continued prednisolone, even at a low dose, may be substantial in high risk patients.

Should tocilizumab, combined with prednisolone (tapered over 26 weeks), become the standard of care in patients with newly diagnosed GCA? In our opinion, this would be premature.

Tocilizumab, a high cost drug, may be better reserved for patients at high risk of corticosteroid complications or those in whom steroid taper during the first few months of therapy is difficult because of disease relapse. Certainly, these data are an important step in providing more options for steroid-sparing and improving the care of patients with GCA.

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