IN BRIEF

THERAPY

Escalating canakinumab for treating NOMID

A 24-month open-label phase I/II trial has shown that the fully human anti-IL-1β monoclonal antibody canakinumab improves symptoms and reduces inflammation in patients with neonatal-onset multisystem inflammatory disease (NOMID). The effect of subcutaneous canakinumab after withdrawal of anakinra therapy was tested in a small group of patients ($n=6$), all of whom experienced post-withdrawal disease flares. Although no patients achieved central nervous system remission (white blood cell count ≤15 per μl cerebral spinal fluid and a reduction in headaches) and they all required maximum dose escalation starting from 150 mg (or 2 mg/kg for <40 kg) every 8 weeks up to 600 mg (or 8 mg/kg if <40 kg) every 4 weeks, two-thirds achieved inflammatory remission (reduction in disease activity and C-reactive protein level ≤10 mg/l).

Original article Sibley, C.H. *et al.* A 24-month open-label study of canakinumab in neonatal-onset multisystem inflammatory disease. *Ann. Rheum. Dis.* doi:10.1136/annrheumdis-2013-204877

RHEUMATOID ARTHRITIS

Etanercept or DMARDs for RA combination therapy?

According to a study of Asian and Latin American patients pooled from the APPEAL ($n=300$) and Latin RA ($n=423$) studies with an inadequate response to methotrexate monotherapy, patients treated with a combination of etanercept and methotrexate ($n=478$) have superior clinical responses at 16 weeks to those treated with a combination of methotrexate and conventional DMARDs (hydrochloroquine [$n=81$], leflunomide [$n=69$] or sulphasalazine [$n=95$]). Superior responses included clinical disease activity index-defined remission (18% vs 7%, $P<0.001$), low disease activity defined by 28-joint disease activity score with erythrocyte sedimentation rate (39% vs 18%, $P<0.001$), and a health assessment questionnaire score ≤0.5 (48% vs 34%, $P<0.001$).

Original article Fleischmann, R. *et al.* Short-term efficacy of etanercept plus methotrexate vs combinations of disease-modifying anti-rheumatic drugs with methotrexate in established rheumatoid arthritis. *Rheumatology (Oxford)* doi:10.1093/rheumatology/keu235

INFLAMMATION

The cardiovascular risk of FMF-related amyloidosis

A cross-sectional study has shown that Turkish patients with familial Mediterranean fever (FMF) associated with nephrotic-range proteinuria and amyloidosis have an increased risk of cardiovascular disease. In comparison with patients with nondiabetic glomerulopathy ($n=102$), patients with FMF-related amyloidosis ($n=98$) had higher serum levels of asymmetric dimethyl arginine (ADMA; median 3.8 vs 2.5 μmol/l, $P<0.001$) and less flow-mediated dilatation (FMD; median 6.0% vs 6.8%, $P<0.001$). Over a 3-year follow-up 25 patients from the group with FMF-related amyloidosis, and only 13 patients with other glomerulopathy, had cardiovascular events. Overall, ADMA and FMD levels were shown to contribute independently to the risk of cardiovascular events.

Original article Yilmaz, M.I. *et al.* Endothelial function in patients with familial Mediterranean fever-related amyloidosis and association with cardiovascular events. *Rheumatology (Oxford)* doi:10.1093/rheumatology/keu231

CONNECTIVE TISSUE DISEASES

Stem cell transplant prolongs systemic sclerosis survival

12-year multicentre trial data now reported in *JAMA* show haematopoietic stem cell transplantation (HSCT) has long-term survival benefits compared with pulsed cyclophosphamide for treating systemic sclerosis (SSc). "No therapy has previously been shown to improve long-term survival," say corresponding authors of the study, Jaap van Laar and Dominique Farge-Bancel, "particularly for those patients with diffuse cutaneous SSc and organ involvement."

The investigator-initiated Autologous Stem Cell Transplantation International Scleroderma (ASTIS) clinical trial began as a European Group for Blood & Marrow Transplantation collaboration with EULAR in the wake of data showing HSCT can improve functional ability and reduce lung, skin and vascular pathology in patients with SSc.

From 2001–2009 patients ($n=156$) with diffuse cutaneous SSc were recruited from 29 centres in 10 different countries for the open label phase III study. Patients were randomized to receive either HSCT ($n=79$) or 12 monthly intravenous injections of pulsed cyclophosphamide ($n=77$).

HSCT involved intravenous injection of filgrastim and cyclophosphamide on two consecutive days before isolation of $CD34^+$ cells from the blood. In preparation for reinfusion of $\geq 2\times10^6$ of these stem cells, patients were conditioned with cyclophosphamide, rabbit antithymocyte globulin, methylprednisolone and hyperhydration.

Switching therapies was prevented for two years, patients were followed-up until 2013, and the primary endpoint was 'event-free survival', a term Alan Tyndall, senior author of the study, defines as "time in days from randomization until either death from any cause or precisely defined persistent endstage major organ failure, such as heart, lung or kidney failure."

"In some patients a complete response was seen, including normalization of skin and loss of all autoantibodies," say the authors. In the first year after treatment there were 13 (16.5%, inc. 8 deaths) adverse events in the HSCT group and 8 (10.4%, no deaths) in the control group. By contrast, after a median follow-up of 5.8 years there were 22 (19 deaths, 3 irreversible organ failures) adverse events in the HSCT group and 31 (23 deaths, 8 irreversible organ failures) in the control group.

These data highlight the importance of long-term trials. "Other studies have shown that if a trial was stopped too soon we would not have known the full risk vs benefit," comments Janet Pope, an independent SSc expert at the University of Western Ontario. "A famous example," she continues "is the tight control for type 1 diabetes mellitus trial."

Although the ASTIS results are positive, Pope notes "this treatment does not apply to the majority of patients with SSc, only those with early diffuse cutaneous SSc who are at risk of doing poorly." However, she says this is a "landmark study" as it might mean "we can find a cocktail treatment with less immune ablation and morbidity to help many more of our patients."

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Original article van Laar *et al.* Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis. *JAMA* doi:10.1001/jama.2014.6368