to achieve long-term B cells depletion. Patients were closely monitored during 46.5 (2–88) months follow-up with clinical and serological surveillance. They received a RTX cumulative dose of 8 g (2–13).

Results—Median serum Ig levels declined continuously – but not gradually – after each RTX re-treatment. The biggest decline in Ig took place after the first RTX round. IgM and IgG levels were below normal in respectively 22 (65%) and 16 (47%) patients – 15 patients (44%) with combined low levels of IgM and IgG – already after the first round.

Eleven patients (29%) had a cumulative CYC dose of 50 g or more and they had lower levels of total Ig after the first 3 RTX rounds and lower levels during RTX maintenance. However the 12 patients (32%) receiving CYC in combination with RTX at induction had bigger overall decline in IgG (3.6 vs 2.2 g/L P = 0.028), IgA (0.78 vs 0.32 g/L P = 0.028), IgM (0.53 vs 0.26 g/L) and total Ig (4.9 vs 2.9 g/L P = 0.030) at last visit compared to those receiving RTX without CYC.

Conclusion—Ig decrease the most after the first RTX round under RTX maintenance. While a high cumulative CYC dose (> 50 g) decreases Ig levels at all time during RTX maintenance, the combination of CYC-RTX at initiation has a synergistic effect with bigger decline of Ig at last visit.

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Treatment

P205

An international, open label, randomised controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis (RITAZAREM)

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Introduction—ANCA associated vasculitis (AAV), includes granulomatosis with polyangiitis (GPA, Wegener’s), microscopic polyangiitis (MPA), and their organ-limited variants. Prior to the availability of effective therapy, AAV had a mortality of 93% within 2 years. The introduction of glucocorticoids (GC) and cyclophosphamide transformed survival, with 5 year survival rates nearing 80%. AAV has become a chronic relapsing disorder. Cumulative exposure to GC and immuno-suppressive drugs contributes to toxicity and organ damage and is of concern to the 50% of patients who relapse within 5 years of initial remission, and the 10% demonstrating a refractory disease course. Novel therapeutic strategies are required for these patients and the 10% of patients intolerant to current treatments.

Methods—RITAZAREM (EudraCT 2012-001102-14; ClinicalTrials.gov NCT01697267) is a parallel, open randomized trial evaluating the efficacy of rituximab (RTX) or azathioprine (AZA) maintenance therapy regimens in patients with relapsing AAV. 190 patients with relapsing AAV will be enrolled at centres across Europe, N America, and Australia to receive RTX (4 x 375 mg/m²), and GC induction therapy. Patients with stable disease at month 4 will be randomised 1:1 to receive repeat RTX or AZA maintenance therapy. All patients will receive GC concomitant with their maintenance regimen. The primary objective is to demonstrate whether or not fixed interval, repeat RTX is superior to AZA in the prevention of disease flare in AAV patients with relapsing disease. The primary endpoint is the time to disease relapse (either minor or major relapse) from randomisation.

Results—RITAZAREM will inform the future standard of care for patients with AAV, and provide data describing long term safety of RTX therapy in AAV patients (Supplementary data).

Discussion—RITAZAREM is a joint venture of the European Vasculitis Study Group and the Vasculitis Clinical Research Consortium. RTX is supplied free of charge by Roche/Genentech.

Further reading


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P206

CSaR inhibitor on leukocytes exploratory ANCA associated renal vasculitis (CLEAR) clinical trial with orally administered CCX168


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Introduction—In ANCA vasculitis, the anaphylatoxin C5a amplifies neutrophil influx and activation through C5aR, leading to renal disease. CCX168, an oral specific CSaR antagonist blocked C5a-induced neutrophil chemotaxis and CD11b expression in human blood samples in Ph1. CCX168 profoundly reduced glomerular crescent formation and necrosis in transgenic hCSaR mice with anti-MPO-induced glomerulonephritis.

Methods—This is a Ph 2 clinical trial at 40 study centers. Patients have GPA, MPA, or renal limited vasculitis, are anti-PR3+ or anti-MPO+, and have renal vasculitis. Patients are randomized 1:2, placebo: 30 mg CCX168 b.i.d. for 12 wks, with 12-wk follow-up. Primary objective: safety and tolerability. Secondary objectives: feasibility of reducing or eliminating corticosteroids (CS), and effect of CCX168 on renal function and ANCA disease. All pts received cyclophosphamide IV induction treatment (15 mg/kg up to 1.2 g). CCX168 pts in Step 1 of the trial started at 20 mg/d prednisone, and placebo pts at 60 mg/d. If Step 1 were successful, Step 2 would commence, where CCX168 pts received no oral CS, and placebo pts a full CS dose. Target enrollment was 12 pts per step.
Results.--Step 1 has been completed. Baseline characteristics of pts in
Step 1: Mean (SD) age 59 (±14) yrs; 6 M/6F; 9 newly diagnosed, 3
relapsed pts; anti-MPO + 7 (58%) pts; anti-PR3 + 6 (50%) pts; mean (SD)
screening s-creat 119.4 (±40.5) μmol/L. No SAEs related to CCX168
occurred in Step 1. No rescue CS was required in the treatment period.
One subject’s disease flared up during the follow-up period. Upon
review, an external data monitoring committee recommended con-
tinuation to Step 2. Eight of 12 pts have been enrolled in Step 2 so far.
One patient’s disease flared up prompting rescue CS. The trial is still
blinded.
Discussion.--The partial CS withdrawal step of this Ph 2 trial has been
completed successfully and the full CS withdrawal step is ongoing.
Conclusion.--The oral CsA antagonist CCX168 could become a new
treatment for patients with ANCA vasculitis.

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P207
Lack of efficacy of tocilizumab in mucocutaneous
Behçet’s syndrome: Report of two cases
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Introduction.-- Behçet’s syndrome (BS) is a rare multisystem
inflammatory disease. The treatment of BS consists of immunomo-
dulating agents and biologics. Tocilizumab, an IL-6 inhibitor, have
shown efficacy in BS patients with resistance to other therapies
disease [1,2].

Methods.--We present hereby two patients of Norwegian ancestry with
severe mucocutaneous BS who failed to respond to treatment with the
IL-6 inhibitor tocilizumab.

Results.--

- A 55-year-old woman was primarily treated with high doses of
glucocorticosteroids with regression of mucocutaneous disease. How-
ever, the addition of colchicine, methotrexate, azathioprine, anti-TNF-a
led to either short efficacy or side effects. After the first infusion of
tocilizumab, a deterioration of mouth and genital ulcers was observed and
the patient was admitted to the internal medicine ward with severe retrosternal pain. The painful responded promptly to a combination
of analgesics and 20 mg of prednisolone.

- A 26-year-old woman with mucocutaneous BS received initially high
to moderate doses of corticosteroids. On the other hand, corticosteroid-
sparing treatment with cyclosporine, azathioprine, colchicine, metho-
trexate, anti-TNF-a led to incomplete response or improper toxicity.
Tocilizumab treatment was started and she received 3 monthly infu-
sions, in total. Partial response was seen during the first two infusions,
however, immediately after the third infusion the painful genital ulcers recurred.

Discussion.--Our report comes in contrast with others that described
efficacy of tocilizumab in severe neurological and oculcar BS. It appears that
IL-6 is a major contributor in the inflammation observed in
neurological and oculcar BS through stimulation of proliferation of Th-17 cells [3]. Nevertheless, in mucocutaneous BS the pathogenesis may
be somewhat different, with different cytokine profile than the other
phenotypes of BS [3]. This may explain the inefficacy of tocilizumab in
mucocutaneous BS.

Conclusion.--Tocilizumab may be ineffective in the treatment of mu-
cocutaneous BS.

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with a humanized anti-interleukin-6 receptor antibody, tocilizumab.

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P208
Improving the quality and safety of intravenous
cyclophosphamide (IV CYC): A regional audit of a
best-practice protocol
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Introduction.--Following the 2009 Department of Health report “Che-
motherapy Services in England: Ensuring quality and safety” a regional
best-practice protocol for the use of IV CYC was developed. The protocol
contains IV CYC regimes with trial evidence, guidance on steroid
tapering and improving host defence. We audited the protocol stan-
dards and outcome of IV CYC use.

Methods.--Retrospective notes review of all patients at three centres
commencing IV CYC between April 2010 and April 2012.

Results.--Sixty-seven patients received IV CYC (41 at Trust 1, 11 at Trust
2 and 15 at Trust 3). Mean age was 59 years. Indications were: Systemic
Vasculitis 37 (GPA 16, EGPA 4, MPA 5, CNS vasculitis 3, other Vasculitis
9); SLE 5; Scleroderma 6; IBD 16; Other CTD 3. Most Vasculitis patients
received the IV CYC protocol currently being used in the MICYC trial. All
SLE patients received the Euro-Lupus regime. Doses were adjusted for
age in 85% and renal function in 100%. Anti-emetics and Mesna were
prescribed in 100%. Counselling and consent were documented in
> 90%. Formal disease activity assessment and vaccinations were
recommended in 48 and 46% respectively, with some variation
between centres.

Twenty-five percent of patients had a documented infection during
therapy, most commonly LRTI or oral candida. Thirty-eight percent
had an adverse event (AE) whilst on CYC; 27% could be attributable to
CYC. The most common AE was nausea ± vomiting in 10%. There were
four deaths during treatment; one could be attributable to CYC. Three
patients did not complete the treatment course (1 withdrew consent, 1
AE, 1 primary inefficacy).

Discussion.--Most patients completed the treatment course. Infections
were common, but usually mild, with no admissions for neutropenic
sepsis. Areas for improvement include: improved formal assessment of
disease activity, documentation of immunization status, and continued
need to communicate with patients and primary care.

Conclusion.--The regional protocol is being followed well in most
domains. It has enabled standard evidence based regimes to be used
across units.

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