decrease in IgG in one third of patients, while in some IgG increased. Factors influencing the rate of change were not confirmed.

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P202
Risk of malignancy with long-term immunosuppression in ANCA-associated vasculitis
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Introduction.– Recent studies indicate that patients with ANCA-associated vasculitis (AAV) have a significantly higher risk of developing malignancies [1], that the mortality in AAV patients is 2.6 times higher than that of the general population, and that malignancies are the second cause of death after the first year of diagnosis [2]. Drawbacks from these studies are a relatively short follow-up, and possibly, under-reportage due to lack of access to registries.

Methods.– We investigated the occurrence of malignancies in 187 histologically confirmed AAV patients after diagnosis at our center between 1982 and 2011 by performing a search in PALGA, a Dutch national pathology database which covers all the histologically confirmed AAV patients after diagnosis at our center.

Results.– One hundred and thirty-six patients with AAV had a follow-up of at least 1 year; 46 of those developed 93 malignancies during a mean follow-up of 12.3 years. There were 63 non-melanoma skin cancers (NMSC) of the skin. Thirteen malignancies occurred more than once: four of the bladder, four of the prostate, three of colon/rectum and two of the lung. There was a variety of one time occurring malignancies. The mean age of AAV patients developing a malignancy was similar to patients without a malignancy (58 years).

Discussion.– This study shows a higher incidence of malignancies than was recently reported for a European study group. One explanation for this discrepancy could be the accurate data reporting through the Dutch PALGA system by which virtually no malignancy could have been missed. There was no significant age difference between patients with and without malignancies. Notably, there was a high number of NMSCs which is most likely related to the immunosuppressive therapy these patients receive. In the management and treatment of patients with AAV, it is of major importance to monitor closely for developing malignancies.

Conclusion.– This study on the development of malignancies after AAV from a large single center experience shows a high incidence of malignancies in AAV patients after diagnosis.

References

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P203
Infectious complications related to treatment in an inception cohort of antineutrophil cytoplasmic antibody associated vasculitis
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Introduction.– The objective of this study was to describe factors associated with infections related to immunosuppression in an inception cohort of patients with biopsy-proven AAV.

Methods.– Four hundred and ninety patients diagnosed with AAV between 1/2000–12/2011, treated with immunosuppressive therapy and not at end stage renal disease (ESRD) on presentation were enrolled. Infectious events within 24 months were assessed.

Results.– Median age was 59 IQR (45,70), 47% female, 54% MPO positive and 25% diagnosed with GPA. Mean follow up was 3.9 ± 3.7 years. Age was increased across infection frequency groups (56 years [43,65] – 0 infections (inf); 60 years [47,71] – 1–2 inf; 64 years [47,72] ≥ 3 inf). More leukopenia events were associated with increasing numbers of infections (1 ± 0.99 l events – 0 inf; 1.24 ± 0.96 events – 1–2 inf; 1.55 ± 1.12 events – ≥ 3 inf; P = 0.03). Relapse episodes were higher across increasing numbers of infections (0.53 ± 0.66 relapses–0 inf; 0.85 ± 0.81 relapses–1–2 inf; 0.95 ± 0.62 relapses–≥ 3 inf; P = 0.001). Greater number of infections within 24 months was associated with a higher likelihood of ever having a severe infection (27 severe infections (22%) – 0 inf; 87 severe infections (41%) – ≥ 3 inf; P < 0.0001). Death from any cause was also associated with more infections (3 deaths (2.5%) – 0 inf; 21 deaths (10%) – 1–2 inf; 9 deaths (10%) – ≥ 3 inf; P = 0.025).

Conclusion.– Higher frequencies of infections within 24 months are associated with death from any cause, development of severe infections, more relapses, more episodes of leukopenia and advancing age.

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P204
Cyclophosphamide effect on immunoglobulins levels in AAV patients treated with long-term pre-emptive rituximab maintenance
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Introduction.– Rituximab (RTX) is an anti-CD20 antibody used in ANCA-associated vasculitis (AAV) for induction and maintenance of remission. The objective of this study is to determine the effect of CYC on Ig levels in patients treated with long-term pre-emptive RTX maintenance.

Methods.– Retrospective study of 38 patients (35 with GPA and with 3 with CSS) treated with RTX between April 2004 and September 2011 for active disease. 58% of the patients had renal involvement. The cumulative cyclophosphamide (CYC) dose was 14 g (0–250). Twelve patients (32%) were treated with combination CYC-RTX at initiation. RTX was initiated as two1 g infusion 2 weeks apart (RA protocol) and thereafter 2 g RTX was administered annually
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 immunosuppressive 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
C5aR 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 C5aR 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 hC5aR 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.

Supplementary data associated with this article can be found on the website of La Presse Médicale (http://www.em-consulte.com/revue/lpm).

Further reading
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