Conclusion.

Methods and results

Polyangiitis.

We report 4 observations of patients with primary Sjögren’s syndrome. About 4 cases

Microscopic vasculitis associated to Sjögren’s syndrome. Besides the well-known vasculitic syndromes, immune or hypersensitivity reactions to medications and foreign materials, direct toxic effects to alveolar capillaries, coagulation defects, hemodynamic and vascular conditions, infectious causes should be taken into account. Identification of different causes and treatment based on the different etiologies are challenging tasks.

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P201 Quantifying the effect of rituximab on changes in serum immunoglobulin G

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Introduction. – Rituximab (RTX) decreases production of pathogenic immunoglobulins in autoimmune disease. Hypogammaglobulinaemia (hypog; IgG < 7 g/L) is a potential complication and assessment of the rate of change in IgG after RTX may assist in the determination of risk factors.

Methods. – Patients receiving RTX for vasculitis or SLE with sequential IgG levels and no subsequent immunosuppressive treatments known to alter IgG were studied. The rate of change in IgG pre- and post-RTX was determined using linear regression. The regression fit was assessed using the Run’s test and visual inspection.

Results. – Sixty-four patients were identified: median age 47 years, 42 female, and 38 (59%) had previously received cyclophosphamide. The median number of data points and the duration of periods of observation were 8 and 23 months pre- (n = 52) and 10 and 25 months post-RTX (n = 64). Compared to the nadir IgG pre-RTX, the incidence of IgG < 7 g/L was increased post-RTX (P = 0.0395), but not for IgG < 5 g/L (P = 0.1765) or IgG < 3 g/L (P = 0.5864). There was an association between the nadir IgG post-RTX and IgG at the time of RTX (P = 0.001). Marked intra-individual variability was observed pre- and post-RTX so temporal IgG trends were not significant in a number of patients. A decrease in IgG was seen in 23 (35%) (in 3/18 IgG was already decreasing pre-RTX), compared to the median rate of change in IgG after RTX may assist in the determination of risk factors.

Discussion. – Linear regression provided an indication of the direction and extent of changes in IgG. RTX was associated with a slow overall decrease in IgG count (nadir on the day 680,000/µL) were demonstrated. On day 6, pt started to complain of shortness of breath and hemoptysis, and from day 8, of fever. Chest X-ray and CT-scan showed diffuse interstitial-alveolar infiltrates. ANCA were confirmed negative as were anti-GBM, anti-DsDNA, anti-phospholipids. Complement fractions were normal. Sputum cultures were repeatedly negative, as was an extensive work up for infectious conditions. Normal valve position and ventricular function were demonstrated by frequent echocardiographic controls. Pt was treated with steroids and supportive care. Pt continued to cough blood until day 19 and 20, when he was treated with nebulized rFVIIa that stopped bleeding.

Autopsy revealed hyperemic lungs at gross examination, with firm gray-brown or pale edematous areas. Histologically pneumonia organizing aspect was prevalent, associated to rare suppurative foci. Only minimal intra-alveolar blood was observed at the periphery of organizing areas. Both septal and interstitial vessels were dilated and congested. Only focal alveolar or interstitial hemosiderin-laden macrophages were present at Pearls stain.

Conclusion. – The clinical spectrum of diffuse alveolar haemorrhage is wider than previously considered. Besides the well-known vasculitic syndromes, immune or hypersensitivity reactions to medications and foreign materials, direct toxic effects to alveolar capillaries, coagulation defects, hemodynamic and vascular conditions, infectious causes should be taken into account. Identification of different causes and treatment based on the different etiologies are challenging tasks.

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Side effects

P201

Microscopic vasculitis associated to Sjögren’s syndrome. About 4 cases

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Introduction. – Glomerular involvement during Sjögren’s syndrome is extremely rare and necessitates an etiological investigation. Hereby, we report 4 observations of patients with primary Sjögren’s syndrome associated to proliferative nephritis related to microscopic polyangiitis.

Methods and results. – The report is about 4 patients whose mean age was 68 years. The first presented with arthritis, the second with lower limb edema, the third and the fourth with paresthesias. All patients reported ocular and oral dryness. Biological investigations revealed in all cases an inflammatory syndrome, a hyperalbuminemia, and a 24-hour-proteinuria over 0.5 g/24 hours. Renal biopsy was performed in 3 cases and revealed diffuse extracapillary proliferative glomerulonephritis with crescents in 1 case and focal segmental glomerulonephritis with crescents in 2 cases. The electromyogram objectified an axonal sensorimotor neuropathy in 3 cases and the nerve biopsy concluded to a necrotizing vasculitis in one case. In all cases, Salivary gland biopsy showed stage 4 chronic lymphocytic sialadenitis according to Chisholm and Mason criteria. The immunological findings revealed positive anti-nuclear antibodies at a rate higher than 1/400 in all cases, as well as positive anti DNA, anti SSA, anti SSb in 3 cases. P-ANCA antineutrophiliccytoxidase antibodies were detected in all cases. The diagnosis of microscopic polyangiitis associated to Sjögren’s syndrome was retained in all cases. All patients underwent a course of corticosteroids associated to 12 monthly pulses of cyclophosphamide relayed by azathioprine. The evolution was favourable in all cases with the mean decline of 40 months.

Conclusion. – Extracapillary proliferative glomerulonephritis with positive p-ANCA in Sjögren’s syndrome is a rare condition and needs to search for an associated systemic vasculitis. In these cases corticosteroids associated to immunosuppressive agents are still the main treatment to ameliorate the renal prognosis.

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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 than that of the general population, and that malignancies are the second cause of death after the first year of diagnosis [2]. Malignancies were the second cause of death in AAV patients [2].

Methods.– We investigated the occurrence of malignancies in 187 historically 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 (NMSC) of the skin. Thirteen malignancies occurred more than once: four of the bladder, four of the prostate, three of colon/rectum and two.

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; 56 severe infections (60%) – ≥ 3 inf; P = c.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 tw1 g infusion 2 weeks apart (RA protocol) and thereafter 2 g RTX was administered annually.

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