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ANCA associated vasculitis – new insight into pathogenesis, diagnostics and therapy**

Nowe spojrzenie na patogenezę, diagnostykę i leczenie układowego zapalenia naczyń związanego z przeciwciałami ANCA

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Słowa kluczowe
ANCA, zapalenie naczyń, patogeneza, diagnostyka, terapia

Summary

ANCA (anti-neutrophil cytoplasmic antibodies) associated vasculitis is common kind of vasculitis. Frequency of this vasculitis increases last years. Both genetic and environmental factors are involved in the pathogenesis of this disease. Uncontrolled neutrophils activation leads to cascade of immunological processes resulting in the vasculitis development. Advanced kidney injury, sclerotic and atrophic changes in kidney biopsy specimens are the risk factors of end-stage renal disease development. Fast diagnosis and kidney biopsy performance are important to plan proper therapeutic scheme. There are many therapeutic regimens used to treat this kind of disease. Standard regimens with steroids and cyclophosphamide in induction remission, and steroids with azathioprine as a maintenance therapy are replaced in some cases by newer schemes with rituximab usage. However all these regimens are connected with adverse effects and there is a need of accurate treatment monitoring and reasonable assessment of the drugs doses for specific patients to protect patients against complications and relapses.

Streszczenie

Układowe zapalenie naczyń związane z przeciwciałami ANCA to jedno z ważniejszych układowych zapaleń naczyń. Częstość tego zapalenia wzrasta w ostatnich latach. W patogenezie tej choroby biorą udział zarówno czynniki genetyczne, jak i środowiskowe. Niekontrolowana aktywacja granulocytów obojętnochłonnych prowadzi do ciągu immunologicznych procesów skutkujących zapaleniem naczyń. Zaawansowana niewydolność nerek, stwardnienie i zmiany zanikowe w biopsji nerki to czynniki ryzyka rozwoju schyłkowej niewydolności nerek. Szybka diagnoza i wykonanie biopsji nerki są ważne we właściwym zaplanowaniu procesu leczniczego. Jest wiele schematów terapeutycznych stosowanych w leczeniu tej choroby. Standardowe schematy z użyciem steroidów i cyklofosfamidu w indukcji remisji i steroidów z azatiopryną w leczeniu podtrzymującym są zamieniane w pewnych przypadkach przez nowsze schematy z użyciem rituksimabu. Wszystkie te schematy są obarczone jednak ryzykiem działań niepożądanych. W związku z tym istotne jest ścisłe monitorowanie leczenia i właściwy wybór dawek leków dla poszczególnych pacjentów, aby uchronić pacjentów przed możliwymi powikłaniami leczenia i nawrotami choroby.

Conflict of interest
Konflikt interesów
None
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INTRODUCTION

ANCA (anti-neutrophil cytoplasmic antibodies) associated vasculitis is according to Chapel-Hill Consensus necrotizing vasculitis, vasculitis with few or no immune deposits, predominantly affecting small vessels (i.e. capillaries, venules, arterioles and small arteries), that is associated with MPO (myeloperoxidase)-ANCA or PR3 (proteinase3)-ANCA. These kinds of antibodies are connected with three types of vasculitis: granulomatosis with polyangiitis-GPA (earlier Wegener's granulomatosis), microscopic vasculitis-MPA and eosinophilic granulomatosis with polyangiitis-EGPA (earlier Churg-Strauss syndrome) (1). This review summarizes current information about ANCA associated vasculitis concerning epidemiology, pathogenesis, diagnostics and therapy.

**Dedicated to Professor Franciszek Kokot outstanding Mentor, Clinician, Researcher.

EPIDEMIOLOGY OF VASCULITIS

Vasculitis type depends on geographical region. Granulomatosis with polyangiitis is more frequent in the northern Europe. Microscopic vasculitis is more common in southern Europe, Japan (2) and in Peru (3), Asians and Maoris in New Zealand (4). Granulomatosis with polyangiitis frequency doubled in Germany between 1994 and 2006. The reasons were probably: increase of disease awareness and more often diagnosis of this disease, increase in survival of patients (5). Frequency of microscopic polyangiitis also increases in Germany (5), Australia (6). The frequency of biopsy proven ANCA (+) vasculitis among people over 18 years old was more than 13.2 million per year. 36 from 82 patients (44%) have died for 12 years of observation (7).

ETIOLOGY

There are many antigens associated with susceptibility to ANCA associated vasculitis. Full list of them may be found in one of the newest publications (8). Very important are also environmental factors, especially infections. Associations between infections: *Pseudomonas*, *Klebsiella, Escherichia coli* (9), *Staphylococcus aureus* (10), *Enterococcus* (11), Ross-River virus (12), Epstein-Barr virus (13), exposure to mRNA in influenza vaccine (14), Rickettsiae (15) infections and development of ANCA associated vasculitis in human were found. Molecular mimicry between fimbrie FimH of *Escherichia coli*, *Klebsiella* and human LAMP (lysosome associated membrane protein) antibodies was also described (16). There was also found that granulomatosis with polyangiitis appearance is cyclical with a period 7.6 years. There was suggested that this disease might be connected with cyclical infection (17). Connections between ambient UVR (ultraviolet radiation) and incidence of granulomatosis with polyangiitis and eosynophilic granulomatosis with polyangiitis were also found (18). Silica is other postulated risk factor of granulomatosis with polyangiitis and microscopic vasculitis (19). Other potential risk factors of c-ANCA positive vasculitis are heavy metal and pesticides exposure, atopy (20), farm exposure (21), drugs. There was also found that microscopic vasculitis is more common in rural than in urban area in Australia (6).

ANCA ASSOCIATED VASCULITIS PATHOGENESIS

ANCA associated vasculitis accordingly with current knowledge develops as a result of neutrophils activation by autoantibodies directed to neutrophils antigens myeloperoxidase and proteinase 3 or against human lysosome-associated membrane protein-2 which is present in neutrophils and vascular endothelium (22). Genetic background promotes development of the disease. At the beginning many environmental factors (infections, stress, lipopolisaccharides and others) may cause priming of neutrophils and complement system activation. As a result of epigenetic changes primed neutrophils exhibit more than normal myeloperoxidase and proteinase 3 on their surface (23) and adhere to endothelium. After that production of ANCA antibodies begins. ANCA antibodies increase priming of neutrophils through Fab and Fc receptor. Primed neutrophils excrete many factors like properdine, B factor, proteases, ROS (reactive oxygen species) and myeloperoxidase. Indicators of neutrophils apoptosis were diminished in the course of ANCA positive systemic vasculitis in comparison with healthy persons (24). As a result vascular endothelium dysfunction appears and alternative complement pathway activation begins including C5a production (25). C5a strongly attracts neutrophils what cause an influx of this kind of cells and induction of severe necrotic vasculitis (26). Moreover in the course of ANCA vasculitis development of NETs (neutrophil extracellular traps) formation appears (27). Products of granulocytes priming especially free radicals promote NETs formation (28). NETs may bind different antigens in chromatin web and activate TLRs (Toll-like receptors) directly (29). TLRs activate lymphocytes Th: TLR9-Th1, and TLR2-Th17 (30). Treg cells function is also impaired in the course of ANCA vasculitis (31). Breg number is diminished without impaired function (in terms of Il-10 production) in the course of ANCA associated vasculitis (32). There is a large number of memory B cells relatively to other B cells during remission in patients with ANCA associated vasculitis. This imbalance may promote big percentage of disease relapses, especially in PR-3 ANCA systemic vasculitis (33). Changes in other kinds of cells function in the course of ANCA associated vasculitis also appear. There was also found that serum from patients with ANCA (+) vasculitis stimulates M2c macrophages podtype to fagocytosis (34). CD14 expression correlated with ANCA autoantigen expression in ANCA vasculitis on monocytes and there were suggestions that it may reflect cell activation (35). Macrophages and dendritic cells were the cells producing chemokine CCL18, antigen that expression is high in crescentic ANCA associated vasculitis and correlates with crescent formation, interstitial inflammation, and impairment of renal function (36). The biomarkers of ANCA positive systemic vasculitis in urine are also searched. It was found that in the course of the disease relapses: alfa-1 acid glycoprotein, KIM-1 (kidney injury molecule 1), MCP-1 (monocyte chemoattractant protein-1), NGAL (neutrophil gelatinase-associated lipocalin) levels increased. MCP-1 levels were the best differentiator of active disease and remission: 1.3 fold increase of MCP-1 was highly associated with relapse of disease (94% sensitivity and 89% of specificity) (37).

DIAGNOSIS

Beginning of ANCA (+) vasculitis from the signs typical for upper respiratory tract infection causes delay in diagnosis of the disease. The fastest diagnosis is when kidneys are involved (38). There is many methods of PR3-ANCA antibodies assessment. Three of them were simultaneously assessed in 78 patients. ELISA with mixture of isolated human PR3-ANCA protein with recombinated protein usage indicated 61% specificity; ELISA with isolated human purified native PR3-ANCA protein usage indicated 81% specificity. Chemiluminescence

had 69% of specificity. These methods did not differ sensitivity (100%). Human purified native PR3-ANCA protein have probably better preserved conformational structure of protein than recombinated PR3-ANCA. This is probably the reason of higher specificity of human purified native PR3-ANCA than recombinated PR3-ANCA (39). The method of c-ANCA antibodies evaluation based on immunofluorescence with algorithmic computer assessment didn't statistically differ in terms of sensitivity and specificity from the visual assessed immunofluorescence ($p > 0.05$) (40). Comparison of DotBlot, Phadia EIA and ELISA indicates that these methods have similar specificity 92-97% in terms of PR-3 and MPO-ANCA antibodies assessment (41). Sometimes MPO-ANCA antibodies may appear in healthy people. MPO-ANCA antibodies in healthy persons have different specificity than MPO-ANCA antibodies in patients with ANCA positive systemic vasculitis (42).

HISTOPATHOLOGY

There was found that in the course of rapidly progressive glomerulonephritis associated with p-ANCA systemic vasculitis diffuse atrophy of tubules is more common than in the patients with c-ANCA systemic vasculitis ($p = 0.01$) (43). Other study describes results of 28 kidney biopsy specimens from the patients with rapidly progressive glomerulonephritis in the course of ANCA systemic vasculitis evaluation. 12 patients (43%) had immunological electron dense deposits present (group A), 16 patients (57%) didn't have immunological complexes deposits present in kidney biopsy specimens (group B). CRP level was lower and lungs were less commonly involved in group A (8.3 vs 56.3%). The proteinuria in the moment of diagnosis was more common in this group (2.46 ± 1.67 vs 0.76 ± 0.52 g/d). Group A was divided into three groups to describe the results of evaluation. Group A was divided into three groups: A1 with mesangial IgA and C3 deposits, A2 with mesangial IgG and C3 deposits, and A3 subepithelial electron dense deposits with IgG and C3 deposits mainly in capillary walls. Patients from group A3 had heavier proteinuria than A1 and A2 groups (44).

PROGNOSIS

Kidneys are commonly involved organs in the course of ANCA (+) systemic vasculitis. As a result of the disease advanced chronic kidney disease may appear. The course of the disease was observed in 203 patients with ANCA (+) vasculitis. The observation time was from 3 to 20 years. In 6% patients end stage renal disease appeared. Prognosis was worse in patients with MPO-ANCA vasculitis than in patients with PR3-ANCA vasculitis (45). The association between PR3-ANCA in granulomatosis with polyangiitis and diseases relapses was found. After the induction of remission free of disease survival was significantly longer in patients with negative PR-3 ANCA antibodies (46). Predictors of ANCA associated systemic vasculitis relapses were high initial serum creatinine concentration, high ESR and presence of myalgia, lungs involvement and lower serum creatinine level (47). The worst prognosis was associated with glomerular sclerosis, tubular atrophy in histopathologic evaluation of kidney biopsy specimens and worse kidney function. Focal changes, crescents and mix changes were connected with better prognosis (48). Rapidly progressive glomerulonephritis with crescents or vascular loops necrosis was not associated with kidney function deterioration in every case. One of the studies describes 38 patients with crescents presence in kidney biopsy specimens assessment. Median creatinine serum concentration was 84 μmol/l and median percentage of glomeruli with crescents or necrosis was 32%. 74% patients had glomerulonephritis associated with ANCA antibodies presence, 18% patients had lupus nephritis, 5% patients had anti-GBM antibodies related disease, 3% patients had hypersensitivity vasculitis. 89% patients had extrarenal manifestation of the disease. All patients were treated. End-stage renal disease appeared in 2 patients within 3 years (49). Crescentic changes are connected with higher risk of end stage renal disease than focal changes (33 vs 5%) in 3 years observation (50).

TREATMENT

For many years standard therapeutic regimen for ANCA systemic vasculitis was usage of cyclophosphamide as an induction (1.5 mg/kg body weight orally) and azathioprine (2 mg/kg m.c.) as a maintenance therapy (51). To optimize therapheutic regimens new approaches are tried. There were many clinical trials involving rituximab usage in ANCA systemic vasculitis treatment performed last years: CYCAZAREM (51), RAVE (52), MAINRITSAN (53). Rituximab used weekly 4 x 375 mg/m^2 (64% remissions) is not interior as to effectivity than 3-months therapy with oral cyclophosphamide (2 mg/kg m.c.) (53% remissions). Moreover rituximab usage in the patients with relapse of systemic vasculitis results in higher rates of remission than cyclophosphamide usage (67 vs 42%) (52). Longer observation of patients (61 from 99 in the rituximab group and 63 from 98 in the cyclophosphamide group) indicates maintenance of complete remission in 48% patients receiving rituximab, without any maintenance therapy, comparing to 39% in patients treated previously with cyclophosphamide that received azathioprine as a maintenance therapy (2 mg/kg m.c.) (54). Rituximab 500 mg at days 0 and 14 and 6, 12 and 18 months more effectively prevents relapses than oral azathioprine used as maintenance therapy after remission achieved with cyclophosphamide (5 vs 29% relapses after 28 months of observation) (53). Remissions after rituximab treatment usually last quite long, even without any maintenance therapy. Highest probability of remission expressed as a percentage was noted when therapheutic schemes with regularly repeated 1 g doses of rituximab were applied. Comparing 4 x 375 mg/m^2 and

2 x 1 g/m^2 in case of relapse scheme versus 2 x 1 g/m^2 and 1 g every 6 months scheme indicated that percentage of remissions was similar in both regimens. Risk of relapse was much lower when higher doses were applied (73 vs 12% after 2 years) (55). Treatment of 172 patients with 1 g rituximab every 4 months (in retrospective analysis) results 100% of complete remissions with 20% probability of relapse (median time to relapse 2.1 years), without mortality increase comparing to general population. Essential decrease of IgG < 400 mg/dl was noted in 10% patients sustained treated with rituximab (22). Risk factors for hypoglobulinemia in patients treated with rituximab was: initial IgG level, previous cyclophosphamide treatment, but not cumulative dose of rituximab (56). Other possible late complication (11.9% of ANCA associated vasculitis patients treated with rituximab) is neutropenia (median time 86 days, range 56-168 days after last dose of rituximab) (57). That was not established how long rituximab treatment is safe, yet. The most adequate moment of change this treatment to maintenance therapy with other drug usage is not known, too. 1 g of rituximab every year allowed to achieve 100% at least partial remissions after 47 months, but acute infections appeared in 26% of patients, chronic infections were noted in 29% of patients. As a result of these complications treatment was ceased in 37% patients. Relapse appeared in 26% of patients mainly as a result of treatment termination (58). The results of this study indicate that adequate dose of rituximab should be arrange to provide maximal remission rate with minimal risk of complications. To arrange adequate dose of rituximab in specific case such parameters like: age, body weight, history of infections, initial IgG level, leucocytosis, previous treatment should be taken into account. Determination of factors influencing effectivity of treatment, relapse risk and adverse events appearance is essential. Small doses of all components diminish the chance of specific drug toxicity. Often control visits, precise monitoring and registering of adverse effects should allow to predict many relapses and adverse effects of treatment before the more serious complications appear.

Last published EULAR/EDTA (European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association) recommendations suggest:

- management of ANCA vasculitis patients in centres of expertise 3C (3 level of evidence, C grade of recommendation),
- performing kidney biopsy in ANCA vasculitis patients 3C,
- induction of remission in life or organ threatening cases using glucocorticoids and cyclophosphamide or rituximab 1A for GPA and MPA, 3C for EGPA,
- induction of remission in non-organ-threatening cases using glucocorticoids and mycophenolate mofetil 1BC (1B is level of evidence, C grade of recommendation) or methotrexate 1BB,
- treatment of major relapse organ or life threatening with a combination of glucocorticoids and either cyclophosphamide or rituximab 1A for GPA and MPA, 3C for EGPA and cyclophosphamide, 3D for EGPA and rituximab,
- plasma exchange should be considered when creatinine level excess ≥ 500 umol/l or 5.7 mg/dl creatinine 1BB and in case of diffuse alveolar haemorrhage 3C,
- for remission maintenance a combination of low-dose glucocorticoids and either azathioprine, rituximab, methotrexate or mycophenolate mofetil is recommended 1BA for GPA and MPA, 3C for EGPA and azathioprine,
- remission maintenance therapy should be continued for at least 24 months following induction of sustained remission 4D,
- patients with refractory cases should be switched from cyclophosphamide to rituximab or from rituximab to cyclophosphamide and managed in expert centres 3C,
- structured clinical assessment is more important than ANCA testing in terms of making decisions about treatment 4D,
- investigation of hematuria in patients previously treated with cyclophosphamide 2BC,
- testing of serum immunoglobulin levels prior to each course of rituximab and in patients with recurrent infection is recommended 3C,
- periodic assessment of ANCA vasculitis patients cardiovascular risk 2BB,
- patients should receive clear explanations about their disease 3C,
- patients should be evaluated for comorbidities associated with ANCA vasculitis 4D (59).

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