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Individualization of the ANCA-associated vasculitis treatment

Indywidualizacja leczenia zapaleń naczyń związanych z przeciwciałami przeciwgranulocytarnymi

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Summary

Vasculitides associated with the presence of anti-neutrophil cytoplasmic antibodies (AAV) are the group of systemic diseases characterized by necrotizing inflammation of small and medium size vessels, without immunologic deposits and presence of circulating specific antibodies. Recent genetics and cohorts study should improve comprehension of pathogenesis of AAV, stratification patients in homogenous group and should progress therapeutic implication.

Immunosuppressive therapy of AAV includes two major periods: first induction of remission, second maintenance therapy. It should be dedicated individually not only depending on the stage and severity of the disease but also on genetic and some prognostic factors. Previous randomized trials and clinical observations show some possible limitations of treatment with cyclophosphamide and steroids. Rituximab seems to be a good alternative in those patients in induction therapy as well as in maintenance therapy.

Streszczenie

Zapalenia naczyń związane z występowaniem przeciwciał przeciwko cytoplazmie granulocytów (AAV) są grupą układowych chorób charakteryzujących się martwiczym zapaleniem małych i średnich naczyń, skąpym występowaniem depozytów immunologicznych lub brakiem takich depozytów oraz obecnością krążących przeciwciał. Najnowsze osiągnięcia w badaniach genetycznych i kohortowych powinny znaleźć odbicie w lepszym zrozumieniu etiopatogenezy AAV, dokładniejszej stratyfikacji pacjentów w jednorodne grupy, a przede wszystkim osiągnięcia te powinny mieć swoje implikacje terapeutyczne.

Leczenie immunosupresyjne AAV obejmuje dwa okresy: indukcję remisji oraz leczenie podtrzymujące. Powinno ono być dostosowane nie tylko do okresu i stopnia ciężkości choroby, lecz także do uwarunkowań genetycznych i czynników decydujących o rokowaniu. Dotychczasowe badania z randomizacją i obserwacje kliniczne wskazują na konieczność ograniczenia stosowania cyklofosfamidu i glikokortykosteroidów oraz częstszego stosowania rytuksymabu zarówno w leczeniu indukcyjnym, jak i podtrzymującym.

The current standards in the treatment of antineutrophil cytoplasmic antibody associated vasculitis (AAV) have been optimized on the basis of a number of randomized studies conducted over the past 20 years and adjusted to the duration and severity of the disease. Unfortunately, they fail to take into account differences in genetic background underlying granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Also, the present recommendations underestimate the extent of kidney damage, the need for dialysis therapy and morphological changes observed in kidney biopsy.

The immunosuppressive therapy of AAV comprises two periods: induction of remission, with a duration be-

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tween 3 and 6 months, and maintenance therapy, lasting 18–24 months as a minimum. In order to induce the remission of AAV, cyclophosphamide (CYP) infusions (15 mg/kg BW) are administered every two weeks, followed by every three weeks, and high doses of glucocorticosteroids (GCC) are used. The induction of remission with cyclophosphamide infusions requires reduction of the dose of the drug according to the age of the patient and the degree of loss of glomerular filtration rate.

The CYCLOPS study spanning over four years compared the outcomes of oral and intravenous cyclophosphamide therapy. There was no difference in patient survival and long-term morbidity, though patients receiving CYP infusions were found to relapse more rapidly [1]. The current goal is to use the lowest possible cumulative doses of CYP, which is ensured by intravenous infusions of the drug. A promising way to induce remission is to combine infusions of rituximab (RTX) with infusions of CYP at lower doses, with a concurrent decrease of the doses of prednisone [2]. Alternatively, induction treatment in early stages of the disease, without renal involvement, can be based on methotrexate (MTX). The NORAM study did not demonstrate any differences in the survival of patients and the incidence of adverse drug reactions between groups of patients treated with MTX or CYP in the induction period [3]. Some studies have shown the suitability of mycophenolate mophetil (MMP) for the induction treatment of AAV [4]. Preliminary findings obtained in the currently ongoing MYCYC study (MMP 2–3 g/day vs. CYP pulses 15 mg/kg BW) indicate a comparable remission rate at 6 months of treatment, and a comparable time to the first relapse of the disease.

High hopes are being pinned on the use of rituximab in the induction treatment of AAV, particularly refractory and relapsing forms of the disease. This is justified because B cells play a major role in the pathogenesis of AAV. Anti-CD20 antibodies cause a depletion of circulating and tissue-resident B lymphocytes [5].

Two randomized clinical trials, RITUXVAS [6] and RAVE [7, 8], categorically confirmed the equivalent efficacy of rituximab and cyclophosphamide in the induction treatment of AAV. In the RITUXVAS trial, subjects received rituximab (4 × 375 mg/m^2 BS) and two pulses of cyclophosphamide (15 mg/kg BW) or pulses of cyclophosphamide (15 mg/kg BW) followed by maintenance therapy with azathioprine (AZA) (2 mg/kg BW). In the RAVE trial, patients were given rituximab (4 × 375 mg/m^2 BS) and glucocorticosteroids with dose tapering until 6 months of treatment or oral cyclophosphamide (2 mg/kg BW a day) for 3–6 months, followed by azathioprine for 12–15 months and glucocorticosteroids. Both trials demonstrated equivalent efficacy of treatment regimens based on RTX and CYP for early-detected MPA and GPA. In addition, the RAVE trial showed a higher remission rate in the relapsing sub-group after treatment with RTX [7]. It must be noted, though, that in the RTX group in both randomized trials cyclophosphamide was either eliminated or reduced, and GCC dosage was decreased early into the trial. An in-depth review of the RAVE-IT trial by Specks et al. revealed that patients treated with RTX for a year received no immunosuppression, and remission of the disease was maintained for 18 months [7]. There is hope, then, that rituximab will make it possible to safely lower the dose of GCC, and either eliminate or reduce the cumulative dose of cyclophosphamide.

In the most severe forms of systemic vasculitides, involving bleeding into pulmonary alveoli and/or a major loss of glomerular filtration rate, plasmapheresis procedures are performed. An analysis carried out by Walsh et al. corroborated the favorable effect of plasmapheresis treatment on the prevention of end-stage renal disease [9]. Intravenously administered CYP with glucocorticosteroids and plasmapheresis treatment can be an effective way of treating severe AVV with an involvement of the kidneys and/or lungs.

Doubts as to the appropriate dose of GCC and the performance of plasmapheresis are expected to be resolved by the currently ongoing multi-centre randomized clinical trial PEXIVAS which includes over 500 patients treated with rituximab or cyclophosphamide in the induction period.

Based on several randomized studies, the principles of maintenance treatment of AAV, which lasts at least 18–24 months, have been established. The treatment is based on small doses of GCC, AZA or MTX. In patients with kidney involvement AZA should be the main drug used in maintenance treatment. In other forms of the disease, the drug equivalent to AZA is MTX. EUVAS recommends MTX at a dose of 20–25 mg/week as a maintenance drug to patients with a normal or slightly impaired kidney function (serum creatinine concentration < 1.5 mg/dl).

Other proposed therapeutic options include leflunomide. Patients with poor tolerance of azathioprine can be treated with mycophenolate mophetil at a dose of 2 g/day as an alternative. Although the IMPROVE study (MMP 2 g/day vs. AZA 2 mg/kg BW) has demonstrated a higher risk of relapse of the disease and a shorter remission period in the group of patients treated with the drug [10], the author believes MMP to be a viable therapeutic option for a specific group of patients. Nevertheless, MMP should not be used as a first-line drug in remission maintenance therapy.

A promising method of maintaining remission is based on rituximab (RTX) infusions administered every 4–6 months. Smith *et al.* published a retrospective study in which remission of the disease was achieved by ad-

ministering 1 g of rituximab with low doses of prednisone (0–40 mg; average dose – 10 mg) every two weeks, following which RTX at a dose of 1 g was used on a routine basis every 6 months for 2 years with a concurrent reduction of the prednisone dose to 2.75 mg [11]. The established two-year rituximab treatment regimen seems to ensure a low disease relapse rate. It is also possible to reduce doses of GCC or withdraw immunosuppression. As there are no biomarkers predicting the relapse of the disease, routine RTX therapy is an effective strategy of maintaining remission. Some researchers, however, advise the monitoring of treatment by assessing blood B-cell counts and levels of immunoglobulin G.

Introducing new, effective and safer therapies will definitely translate into improved prognosis in patients with AAV. However, new treatments must take due account of pathogenetic differences existing between the diseases, the duration of the condition and extent of damage to body organs including morphological changes in renal glomerulus and interstitium.

Consequently, attempts should be made to achieve further individualization of AAV treatment. Induction treatment should be based on cyclophosphamide infusions and/or rituximab. In the most severe forms of the disease, plasmapheresis is recommended. Also, a reduction in glucocorticosteroids is indicated. The most important drugs in maintenance treatment are: azathioprine, methotrexate with low doses of GCC or without GCC. A promising method of maintaining remission involves routine rituximab infusions. Other therapeutic options require further studies to determine their efficacy and safety.

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