Prevention of infections in patients with antineutrophil cytoplasm antibody-associated vasculitis: potential role of hydroxychloroquine

In a recent observational study, Kronbichler *et al* recorded 95 severe/life-threatening infections in 49 of 192 patients (25.5%) with associated vasculitides (AAV) within approximately 2 years following rituximab initiation.[1] Respiratory tract infections were the most common infectious complications. In patients with a positive culture, opportunistic pathogens were frequently seen, though *Pneumocystis jirovecii* was identified in only one case.

Trimethoprim/sulfamethoxazole prophylaxis was administered in 73 of 192 patients (38.0%) and resulted in an impressive reduction in the risk of severe infectious complications by 70%. Approximately half of patients were treated with 480 mg or 960 mg on alternate days. The optimum prophylactic dose of trimethoprim/sulfamethoxazole in patients with non-HIV remains unknown. The current recommendations for the management of AAV encourage prophylaxis against *P. jirovecii* infection with trimethoprim/sulfamethoxazole 960 mg on alternate days or 480 mg daily in all patients being treated with cyclophosphamide, where not contraindicated.[2] There is some evidence suggesting that a lower dose of trimethoprim/sulfamethoxazole may be equally effective and more safe than 480 mg daily. In a randomised controlled 52-week trial involving 183 patients with systemic rheumatic diseases, daily administration of 240 mg of trimethoprim/sulfamethoxazole for the prophylaxis of Pneumocystis pneumonia was as effective as daily single-strength dose of 480 mg and was shown to be superior in safety.[3]

Trimethoprim/sulfamethoxazole can cause serious adverse events. However, in patients with rheumatic diseases exposed to prolonged high-dose glucocorticoid its benefit outweighs a potential harm. In Kronbichler *et al* study, 5 of 73 patients (6.8%) stopped trimethoprim/sulfamethoxazole due to adverse events. Nevertheless, the majority of patients were able to continue trimethoprim/sulfamethoxazole prophylaxis during the 2 year observation (mean 14.7 months).

Trimethoprim/sulfamethoxazole is probably not the only medication that can be routinely used for the prevention of infections in patients with AAV and other rheumatic diseases. Accumulating evidence suggests that antimalarials can have a protective effect against infectious complications in patients with systemic lupus erythematosus (SLE). Feldman *et al* studied the epidemiology of serious infections in a nation-wide cohort of 33 565 patients with SLE.[4] Hydroxychloroquine users had a reduced risk of infection as compared with never users (HR 0.73, 95% CI 0.68 to 0.77). A negative association between duration of antimalarials use and severe infections was also observed in the Spanish cohort of 3658 patients with SLE, though in this study the protective effect was small.[5] In vitro studies indicate that chloroquine/hydroxychloroquine have a broad spectrum of activity against different bacteria, fungi and viruses at clinically achievable plasma concentrations.[6] Although the available data are scarce, the susceptibility of *P. jirovecii* to chloroquine in tested concentrations was shown in the infected human lung fibroblasts,[7] while in a double-blind, randomised clinical trial another antimalarial primaquine in combination with clindamycin were similar in efficacy to trimethoprim-sulfamethoxazole for treatment of mild to moderate Pneumocystis pneumonia in patients with acquired immune deficiency syndrome.[8] We follow a 25-year-old female patient with Takayasu arteritis who developed Pneumocystis pneumonia during treatment with infliximab. Administration of trimethoprim/sulfamethoxazole was complicated by severe bronchial obstruction. Pentamidine or atovaquone is not available in Russia. Two weeks treatment with clindamycin 900 mg daily and hydroxychloroquine 600 mg daily resulted in rapid recovery and radiographic resolution of pneumonia. Subsequently, she continued to take hydroxychloroquine for 2 years.

Hydroxychloroquine may control constitutional symptoms, decrease the risk of lupus flares and organ damage, spare the dosage of corticosteroids, prevent the thrombotic effects of antiphospholipid antibodies and increase the life expectancy of patients with SLE. In a recent meta-analysis of 19 studies involving 19 679 participants, chloroquine/hydroxychloroquine use was associated with a significantly reduced risk of cardiovascular disease.[9] Recently, Casian *et al* reported the successful treatment with hydroxychloroquine in a few patients with AAV and other systemic vasculitides[10] and proposed a phase II 52 week, double-blind, randomised placebo-controlled trial in adult patients with AAV who continue to have active disease after remission-induction therapy (Hydroxychloroquine in antineutrophil cytoplasmic antibody (ANCA) Vasculitis Evaluation—HAVEN). The investigators aim to demonstrate that addition of hydroxychloroquine to standard maintenance therapies may improve vasculitis activity, morbidity and quality of life.

In summary, severe infectious complications are common during treatment with rituximab in patients with AAV. Kronbichler *et al* showed that routine use of trimethoprim/sulfamethoxazole might be justified in rituximab-treated patients. Regarding dosing of trimethoprim/sulfamethoxazole, physicians should probably follow the 2016 European League Against Rheumatism (EULAR)/European Renal Association—European Dialysis and Transplant Association (ERA-EDTA) recommendations for patients being treated with cyclophosphamide, that is, 960 mg on alternate days or 480 mg daily. We speculate that hydroxychloroquine may also decrease the risk of infectious complications and may confer additional benefits to patients with AAV. We suggest that serious infections rate may be an additional secondary endpoint in HAVEN or similar trials. Recently, MAINRITSAN2 study results showed that reduced exposure to rituximab was not associated with an impaired efficacy of maintenance therapy in patients with AAV. Therefore, less intensive regimens of rituximab administration, that is, fever infusions or lower doses, may be another approach to improving safety of treatment.

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REFERENCES

1 Kronbichler A, Kerschbaum J, Gopaluni S, *et al*. Trimethoprim-sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis. *Ann Rheum Dis* 2018;77:1440–7.
2 Yates M, Watts RA, Bajema IM, *et al*. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis* 2016;75:1583–94.
3 Utsunomiya M, Dobashi H, Odani T, *et al*. Optimal regimens of sulfamethoxazole-trimethoprim for chemoprophylaxis of Pneumocystis pneumonia in patients with systemic rheumatic diseases: results from a non-blinded, randomized controlled trial. *Arthritis Res Ther* 2017;19:7.
4 Feldman CH, Hiraki LT, Winkelmayer WC, *et al*. Serious infections among adult Medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. *Arthritis Rheumatol* 2015;67:1577–85.
5 Rúa-Figueroa Í, López-Longo J, Galindo-Izquierdo M, *et al*. Incidence, associated factors and clinical impact of severe infections in a large, multicentric cohort of patients with systemic lupus erythematosus. *Semin Arthritis Rheum* 2017;47:38–45.
6 Rolain JM, Colson P, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. *Int J Antimicrob Agents* 2007;30:297–308.
7 Bartlett MS, Eichholtz R, Smith JW. Antimicrobial susceptibility of Pneumocystis carinii in culture. *Diagn Microbiol Infect Dis* 1985;3:381–7.
8 Safrin S, Finkelstein DM, Feinberg J, *et al*. Comparison of three regimens for treatment of mild to moderate Pneumocystis carinii pneumonia in patients with AIDS. A double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. ACTG 108 Study Group. *Ann Intern Med* 1996;124:792–802.
9 Liu D, Li X, Zhang Y, *et al*. Chloroquine and hydroxychloroquine are associated with reduced cardiovascular risk: a systematic review and meta-analysis. *Drug Des Devel Ther* 2018;12:1685–95.
10 Casian A, Sangle SR, D'Cruz DP. New use for an old treatment: hydroxychloroquine as a potential treatment for systemic vasculitis. *Autoimmun Rev* 2018;17:660–4.