Response to: 'Prevention of infections in patients with antineutrophil cytoplasm antibody-associated vasculitis: potential role of hydroxychloroquine' by Novikov *et al*

We thank Dr Novikov *et al* for their letter on the risk of infections of patients with antineutrophil cytoplasm antibody (ANCA)-associated vasculitis and the proposed beneficial effects of hydroxychloroquine (HCQ) to reduce severe infections, as a response to our recently published article 'Trimethoprim-sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis'.[1 2]

Modern therapies and adoption of treatment protocols have improved outcome of patients with ANCA-associated vasculitis. Morbidity and mortality, either attributable to the disease or immunosuppressive measures, remain a challenge for the treating physician. A recent meta-analysis of observational studies found a 2.7-fold increased risk of death with a trend towards improved mortality rates in more recent cohorts.[3] Among patients recruited into the 'early trials' conducted by the European Vasculitis Society (EUVAS), 133 (25%) deaths were recorded over a median follow-up period of 5.2 years. Main causes for death were infections (48%) and active vasculitis (19%) in the first year, while infectious complications remained one of the leading complications leading to mortality (20%) thereafter. Moreover, infections were the leading contributing factor of mortality in this period.[4] Several risk factors leading to infections have been identified in the pre-rituximab era, namely steroid exposure, older age, higher baseline creatinine or dialysis dependency, low lymphocyte count, pulmonary involvement and a rapid fall in the ANCA titre, the latter presumably as direct consequence of a more aggressive immunosuppressive regimen.[5] No such risk factors have been identified in rituximab-treated patients.

Our study[2] identified several independent risk factors to develop severe infections defined as Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grade 3 and above following rituximab initiation. We found an association with older age, endobronchial involvement, chronic obstructive pulmonary disease and prior alemtuzumab use, while trimethoprim-sulfamethoxazole reduced the risk of severe infections by 70%. An overall event rate of 26.06 per 100 person-years was reported with no clear association of an increased risk during the first months of therapy.[2] The high number of infections merits further efforts to reduce infectious complications in patients with ANCA-associated vasculitis.

We agree with Novikov *et al* that trimethoprim-sulfamethoxazole should be used for the prevention of infections in patients with ANCA-associated vasculitis receiving induction treatment,[1] but more data are required to confirm our findings. As mentioned, the ideal dosage of trimethoprim-sulfamethoxazole is unknown and severe adverse events have been reported, including the onset of Stevens-Johnson syndrome, as also discussed in the letter by Wallace *et al*[6] and our response.[7] In patients receiving high doses of steroids, trimethoprim-sulfamethoxazole reduced the risk of *Pneumocystis jirovecii* and its related mortality. Adverse events attributable to trimethoprim-sulfamethoxazole occurred in 32 patients, corresponding to 21.2/100 person-years.[8] A study investigating efficacy of different trimethoprim-sulfamethoxazole doses to prevent *P. jirovecii* assigned patients to either 400/80 mg daily (SS group), 200/40 mg daily (HS group) or an escalation group with a starting dose of 40/8 mg daily and an increase to 200/40 mg daily (ES group). The rate of serious adverse events was similar and the number of deaths numerically higher in the HS group. However, the overall adverse event rate of the SS group was increased compared with the other groups.[9] Although Novikov *et al* argue for the potential of a dose-reduced chemoprophylaxis,[1] firm conclusions from this non-blinded study performed in Japanese patients with rheumatic diseases are not possible to draw.

Antimalarials, namely chloroquine and HCQ, have been recommended in the management of patients with systemic lupus erythematosus.[10] Both agents have anti-inflammatory, immunomodulating, antithrombotic, metabolic, antitumour and anti-infective properties and are currently tested in several clinical trials testing different indications.[11] In a recent systematic review, patients with lupus nephritis and antimalarial exposure showed a lower likelihood to develop end-stage renal failure, hypertension, thrombotic events, infections and deaths.[12] A large study focusing on major infections, defined as disseminated infections, affecting deep organs, requiring hospitalisation or causing death, found a 94% reduction of infectious complications in those receiving antimalarials.[13] Analysis of serious infections, defined as any infection requiring hospitalisation or the use of intravenous antimicrobial agents, found a protective role of HCQ use to reduce infection-related mortality.[14] Feldman *et al* used the Medicaid Analytic eXtract database and identified 33 565 patients, of whom 5078 had 9078 infectious complications. As expected, patients with lupus nephritis were at increased risk. Both groups, those with or without lupus nephritis, had a reduction of infections when HCQ was used.[15]

But how can these data be translated to ANCA-associated vasculitis? No such data exist for ANCA-associated vasculitis. Experience from a single centre on the use of HCQ in eight patients with ANCA-associated vasculitis was recently reported. A benefit was reported by six and two patients were unsure about efficacy of HCQ. No reports regarding safety have been stated by the authors, but a randomised controlled trial of HCQ (HAVEN; EudraCT Number—2018-001268-40) has received funding by the Medical Research Council UK which will address both, safety and efficacy outcomes, in patients with ANCA-associated vasculitis.[16]

We agree that efforts are needed to reduce comorbidities of patients with ANCA-associated vasculitis. Given the pleiotropic effects of HCQ, this agent may have an impact on future treatment protocols of ANCA-associated vasculitis and may reduce the burden of thrombosis, cardiovascular events, malignancy risk and most importantly infectious complications. Randomised controlled trials like the HAVEN study (HCQ in ANCA vasculitis evaluation) are on the way and may pave the way for such protocols.

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