Extended follow-up after stopping mepolizumab in relapsing/refractory Churg-Strauss syndrome

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ABSTRACT

Object. *To report on the extended follow-up of relapsing/refractory CSS patients treated with mepolizumab with respect to relapse rates.*

Methods. *The follow-up consisted of regular clinic visits of patients who received nine infusions of mepolizumab (750mg IV) and switched to methotrexate 0.3mg/kg for maintenance of remission. Glucocorticoids were maintained as low as possible. Disease activity was measured using the Birmingham Vasculitis Activity Score (BVAS). Disease states as remission or relapse were defined according to the EULAR/EUVAS recommendations. The serum eosinophil cationic protein (ECP) was measured regularly and concentrations were correlated with BVAS.*

Results. *The follow-up of the study population under standard methotrexate maintenance therapy was extended to a median of 22 months. Three of nine patients were still in remission at the end of follow-up. During this time five major relapses in three and seven minor relapses in five out of the total nine patients were recognised. ECP levels were found to correlate stronger with the BVAS ($r=0.38$; $p<0.0001$) than other measures such as eosinophil counts.*

Conclusion. *After induction of remission with mepolizumab the majority of patients suffered relapses when switched to methotrexate maintenance therapy. These data suggest that patients with CSS may require long term treatment with mepolizumab. Future trials in CSS should use other doses or dosing intervals for patients in remission. ECP is a promising marker of disease activity in CSS.*

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Competing interests: none declared.

Introduction

We recently reported on the use of mepolizumab, an IL-5 antibody, for the treatment of refractory or relapsing Churg-Strauss syndrome (CSS) (1). While this antibody induced remission in nine out of ten patients, switching to methotrexate maintenance therapy led to several relapses after a median follow-up of ten months. Here we report on the extended follow-up of this trial population. We wanted to find out whether stabilisation occurs after a longer period of methotrexate treatment as it is well now that this drug needs several weeks to develop its full effect. We further wanted to investigate if those patients who were still in remission at the end of the first follow-up period achieved long-term remission. The potential of mepolizumab to induce long-term remission in CSS patients with a history of frequent relapses is not known. The close monitoring during the trial phase was also used to evaluate potential new makers of disease activity, especially the eosinophil cationic protein (ECP). Peripheral blood eosinophil counts are no reliable surrogate for disease activity as they are very sensitive to glucocorticoid (GC) treatment and drop rapidly in response to medium to high GC doses. As shown in earlier trials in CSS but also in the Hypereosinophilic Syndrome (HES) mepoplizumab also leads to a rapid clearance of eosinophilis from peripheral blood (1-3). However, clinical experience suggests that damage in CSS can occur in the absence of eosinophils in peripheral blood. It is likely that eosinophil tissue infiltrates show a slower response to medication. Furthermore, biopsy studies have shown that eosinophils tend to disintegrate fast becoming identifiable only by their remains (4). Since ECP is a major protein of eosinophils and is released during disintegration it can be detected in serum or plasma. Thus, ECP seems a promising candidate marker in CSS and possibly reflects the whole "eosinophil load" of the body (5). Indeed there are earlier reports on higher ECP serum levels in active *vs.* inactive CSS (6,

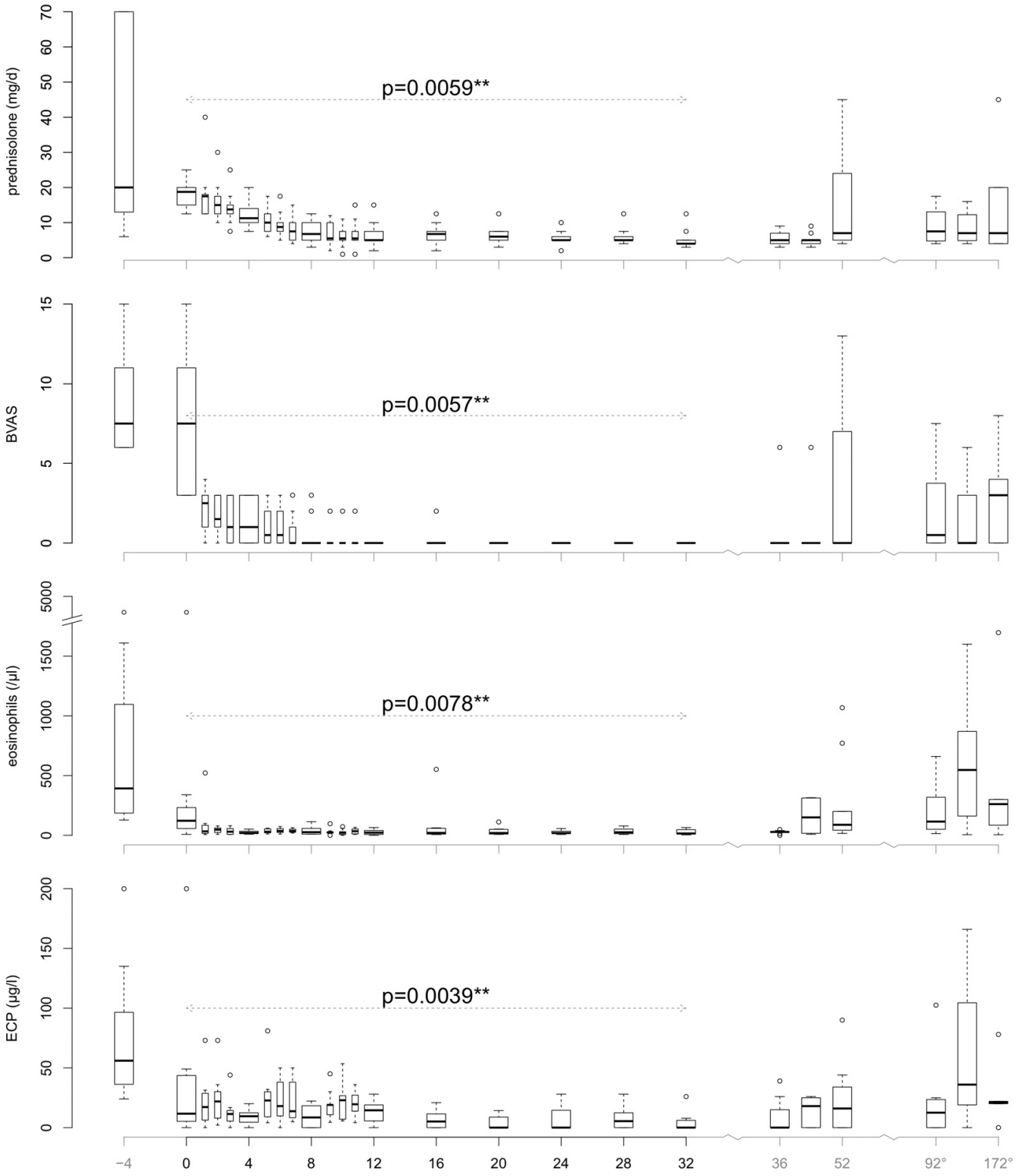

Fig. 1. Box plot of the changes during the course of the study: prednisolone dose (first line), Birmingham Vasculitis Activity Score (BVAS, second line), absolute eosinophil count in peripheral blood (third line), and serum concentration of the eosinophilic cationic protein (ECP, fourth line). Outliers are depicted as o.

7). In this extension study we wanted to correlate ECP serum levels with the established measure of disease activity, *i.e.* with the Birmingham Vasculitis Activity Score (BVAS) (8).

Patients and methods

Patients included in the original trial of mepolizumab (1) in refractory or relapsing CSS were followed in repeated visits for re-evaluation. A clinical and laboratory work up was performed at each visit and BVAS scores were calculated as described (1). According to the protocol mepolizumab was stopped after nine 750 mg infusions and pa-

Table I. Relapses after stopping mepolizumab.

Patient number	Days after last infusion	Clinical manifestation
Major relapses		
2	848	eosinophilic alveolitis (31% in bronchoalveolar lavage), rhinitis
5*	137	re-occurrence of ventricular arrhythmia, progressive neuropathy
7*	139	eosinophilic alveolitis (11% in bronchoalveolar lavage), sinusitis
7	307	alveolar haemorrhage
Minor relapses		
1*	290	sinusitis
1	695	sinusitis, rhinitis
2*	176	arthralgia, constitutional symptoms
3	858	progressive neuropathy
7*	27	sinusitis, rhinitis
7*	529	sinusitis, rhinitis
9*	223	sinusitis, constitutional symptoms

Relapses that already have been reported (1) are marked with*.

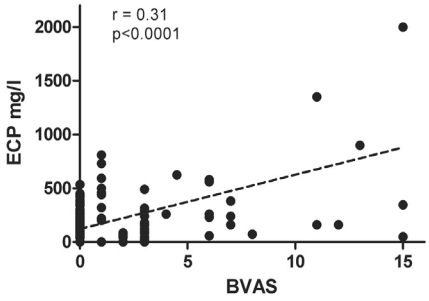

Fig. 2. Correlation between the Birmingham Vasculitis Activity Score (BVAS) and the serum concentration of the eosinophilic cationic protein.

tients were switched to methotrexate (MTX) 0.3mg/kg BW for maintenance of remission. GCs were kept as low as possible according to the judgment of the patient and the treating physician. In this phase there was no fixed steroid scheme.

Definitions to describe disease state and activity were used as given by the EULAR/EUVAS (9).

All patients gave written informed consent and the original trial was registered under NCT00716651. The local ethics committee approved the study.

ECP serum levels were measured at each visit during the active treatment phase as well as during follow-up. The UniCAP 100 E test was used (Phardia, Freiburg, Germany).

For statistical analysis the GraphPad Prism 5 Software (GraphPad Software, La Jolla, USA) was used. The *t*-test for paired samples and the spearman correlation were used as appropriate. *P*-values <0.05 were considered significant.

Results

Ten patients were included in the initial study as described. For individual patient characteristics and outcomes during the ten-month follow-up see (1). At week 32 nine patients were switched to MTX (0.3 mg/kg BW) plus GC according to the protocol. The median follow-up now was 22 month (range 7 to 30). Three of nine patients were still in remission at the end of this study (last visit at weeks 79, 134 and 143). In addition to the already reported relapses two other major and two minor relapses occurred (see Table I). The mean eosinophil counts rose after stopping the anti-IL-5 medication and in six of the nine patients GC-doses had to be increased above 7.5 mg/d. The main findings are depicted in Figure 1.

In the pooled data of all patients there was a highly significant correlation between the BVAS scores and ECP levels (r=0.31; $p<0.0001$, Figure 2). When looking at individual patients a significant correlation between BVAS and ECP was found in four cases. There also was a correlation between eosinophil counts and ECP (r=0.36; $p<0.0001$) and between BVAS and eosinophil counts (r=0.28; $p<0.0001$).

Discussion

Our initial study of mepolizumab in refractory and relapsing CSS demonstrated the potential of mepolizumab to induce and maintain remission (1). We also confirmed the steroid sparing properties of this anti-IL-5 treatment shown earlier in HESs (2, 3). The follow-up data presented here provides further support on how future use of mepolizumab in CSS may be recommended. In light of the high relapse rate after stopping mepolizumab it seems not advisable to use it only for induction of remission. Therefore, the well established principle of the sequence of induction of remission followed by maintenance, *e.g.* with MTX (10) therapy that clearly is beneficial in GPA and MPA (11) may not be optimal in CSS. Amongst many other evidences including genetic studies this underlines the differences between the conditions subsumed under the expression of AAV (12). On the other hand the finding that three patients reached long term remission argues against an illimitable use of mepolizumab, particularly with regard to the still lacking long-term safety data. Instead of cessation of the medication, slow dose reduction or alternatively prolongation of application intervals seems rational. However, the question will be which parameter should guide these therapy changes. To date, there is no reliable marker sufficiently indicating increasing disease activity prior to clinical manifestations. Especially, in treated patients eosinophil counts do not necessarily reflect activity. In our actual -but also in earlier- cohorts even major relapses were accompanied only by mild increases. As serum-ECP was shown earlier to be increased in active vs. inactive CSS (6, 7) it seemed reasonable to try to correlate this parameter with measures of disease activity. The BVAS, although not perfectly suitable for CSS, is the only established composite index for this purpose. In this work the correlation between BVAS and ECP was stronger than that for BVAS and eosinophil counts. However, due to the low number of patients and the relatively long time intervals between the visits it is not clear whether or not increase in ECP might precede disease flares and therefore could be used to guide preemptive therapy.

References

1. MOOSIG F, GROSS WL, HERRMANN K, BREMER JP, HELLMICH B: Targeting interleukin-5 in refractory and relapsing Churg-Strauss syndrome. *Ann Int Med* 2011; 155: 341-3.
2. KIM S, MARIGOWDA G, OREN E, ISRAEL E, WECHSLER ME: Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. *J Allergy Clin Immunol* 2010; 125: 1336-43.
3. ROTHENBERG ME, KLION AD, ROUFOSSE FE *et al*.: Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med* 2008; 358:1215-28.
4. HATTORI N, ICHIMURA M, NAGAMATSU M *et al*.: Clinicopathological features of Churg-Strauss syndrome-associated neuropathy. *Brain* 1999; 122: 427-39.
5. BYSTROM J, AMIN K, BISHOP-BAILEY D: Analysing the eosinophil cationic protein – a clue to the function of the eosinophil granulocyte. *Respir Res* 2011; 12: 10.
6. SCHMITT WH, CSERNOK E, KOBAYASHI S, KLINKENBORG A, REINHOLD-KELLER E, GROSS WL: Churg-Strauss syndrome: serum markers of lymphocyte activation and endothelial damage. *Arthritis Rheum* 1998; 41: 445-52.
7. GUILPAIN P, AUCLAIR JF, TAMBY MC *et al*.: Serum eosinophil cationic protein. A marker of disease activity in Churg-Strauss syndrome. *Ann NY Acad Sci* 2007; 1107: 392-9.
8. LUQMANI RA, BACON PA, MOOTS RJ *et al*.: Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *QJM* 1994; 87: 671-81.
9. HELLMICH B, FLOSSMANN O, GROSS WL *et al*.: EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. *Ann Rheum Dis* 2007; 66: 605-17.
10. REINHOLD-KELLER E, DE GROOT K: Use of methotrexate in ANCA-associated vasculitides. *Clin Exp Rheumatol* 2010; 28: S178-82.
11. MUKHTYAR C, GUILLEVIN L, CID MC *et al*.: EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis* 2009; 68: 310-7.
12. ARNING L, HOLLE JU, HARPER L *et al*.: Are there specific genetic risk factors for the different forms of ANCA-associated vasculitis? *Ann Rheum Dis* 2011; 70: 707-8.