L6. Eosinophilic granulomatosis with polyangiitis: Future therapies

Is EGPA an entity?

Eosinophilic granulomatosis with polyangiitis (EGPA) as the rarest form of ANCA-associated vasculitis (AAV) has several specifics making classification difficult. For good reasons, EGPA is classified amongst the AAVs and it shares features with Microscopic polyangiitis (MPA) and with Granulomatosis with polyangiitis (GPA). However, the prevalence of ANCA is lowest in EGPA and ANCA tend to become negative under therapy much faster than seen in the other AAVs [1,2]. Furthermore, there is substantial evidence that ANCA-negative and ANCA-positive EGPA differ in their clinical presentation, with ANCA-positive patients tending to more “vasculitic” manifestations as glomerulonephritis whereas cardiac-involvement is seen more often in ANCA-negative EGPA [1,3,4]. EGPA and the other AAVs differ also concerning their genetic background. For example, some single nucleotide polymorphisms can be risk factors in GPA but seem to be protective in EGPA [5]. Furthermore, as a relevant portion of its pathology results from tissue hypereosinophilia and most EGPA patients fulfill the “classical” Chusid-criteria for the hypereosinophilic syndromes (HES) [6], according to recent consensus statements EGPA can also be classified as a form of HES [7]. This opening remarks are important when thinking about future therapies in EGPA: it seems likely that with the availability of data from larger cohorts and ongoing genotype and phenotype analysis it will turn out that there is no single entity EGPA but a broad spectrum of conditions ranging from typical AAV-like phenotypes with predominant vasculitic manifestations to forms in which tissue-hypereosinophilia is the leading pathological mechanism as in the HESs. The exact determination of the individual disease phenotype will therefore become important for the choice of the optimal therapy and strategies both from AAV- and from HES-trials may be applied.

New EGPA therapies in the near future

Rituximab

Today, EGPA usually is treated according to the same principles of induction of remission and maintenance of remission using glucocorticosteroids (GC) and conventional immunosuppressants as the other AAVs. In this field, the use of rituximab (RTX) is the most relevant recent development. It is now widely accepted that in the treatment of MPA and GPA, RTX can be used as substitute for cyclophosphamide (CYC), although clear superiority of RTX over CYC as well as the postulated benefits concerning adverse reactions have not been formally proven. In the relevant trials that led to approval of RTX by the FDA, EGPA patients have not been included [8]. However, there are some case reports and some small case series suggesting that RTX might also be effective in EGPA. Most of those reports deal with patients refractory to standard induction of remission. In a few cases, good efficiency has also been demonstrated in non-refractory patients. In the latter the reason for using RTX instead of CYC usually was the wish to conserve fertility [9]. In GPA it has been demonstrated that vasculitic manifestations show a better response to RTX than the granulomatous manifestations [10]. From the available data it might be speculated that comparably in EGPA manifestations due to eosinophilic tissue infiltration respond different than “pure vasculitic” phenomena. Although it is obvious that such observations would lead to a more differentiated use of RTX in EGPA, the current database is not sufficient to support such an approach. It seems likely that RTX will be used for induction of remission in EGPA more often in analogy to the other AAVs, although data from controlled trials will not be available soon. About a possible role of RTX for maintenance of remission, the lack of data is even larger and no data based statements can be made.
Anit-IL-5

Interleukin-5 (IL-5) is one of the most important cytokines in the induction and promotion of hypereosinophilia. Increased IL-5 production has been shown in stimulated peripheral blood mononuclear cells from EGPA patients [11]. A randomised controlled trial of a monoclonal antibody against IL-5, mepolizumab, in HES demonstrated a significant reduction in the GC-need and prompt normalization of peripheral blood eosinophil counts [12]. The drug also showed efficiency in other eosinophilia-related conditions as eosinophilic asthma or eosinophilic- esophagitis [13,14]. There are two small pilot studies of mepolizumab in EGPA with a total of 17 treated patients [15,16]. In both studies mepolizumab allowed for GC reduction and reduced disease activity. In one of the studies eight of 10 patients with refractory or relapsing EGPA reached remission [15]. After stopping the drug in most of the patients, the disease activity increased again [17]. Therefore, it seems that a future anti-IL-5 strategy should also include aspects of maintenance of remission. In all published trials on mepolizumab the safety profile was favourable. On the bases of this data a randomised controlled trial with mepolizumab in EGPA is desirable. In case mepolizumab will be approved for other indications and therefore would be available on the market off-label use in selected cases may be justifiable. There are further anti-IL-5 drugs under investigation that might also be of interest. However, till now there is no data in EGPA.

**Immunological considerations and new therapeutic options**

EGPA is usually considered to be Th2 dominated condition. Several drugs targeting Th2-cytokines and receptors are now under development and investigation. Asthmatic patients are one of the groups in the focus of the pharmaceutical industry. Two prominent examples out of a vast spectrum of drugs under development are lebrikizumab and pitrakinra. An IL-13 antibody, lebrikizumab, was effective in asthma patients and it was speculated that this drug let to decreased recruitment of eosinophils to the lungs and the airways. A slight increase in peripheral blood eosinophil counts was observed [18]. Further investigations are needed to prove this mechanism which then could be attractive for EGPA patients as well. Pitrakinra, a modified IL-4 that binds to but does not activate IL-4/IL-13 receptors, showed efficiency in asthma. Blood eosinophil counts did not change with this drug but exhaled nitric oxide levels, which reflect airway inflammation, went down [19].

Regulatory T-cells play a significant role in EGPA. Low numbers of peripheral blood regulatory T-cells (Treg) are associated with relapses, whereas high numbers are associated with remission [20]. A comparable situation has been described in hepatitis-C induced vasculitis. In those patients, very low doses of interleukin-2 led to increased Treg-counts and subsequent clinical improvement [21]. In an animal model of autoimmune neuritis expansion of Tregs with recombinant IL-5 led to substantial clinical improvement [22]. Both works demonstrate that modulation of Tregs might be a new approach to autoimmune diseases and might be especially suitable for EGPA. However, prior to a first clinical use several open questions will have to be addressed, e.g. which is the optimal (low) dose of IL-2 and how can blocking of IL-5 be effective as well as treating with IL-5. In conclusion, it is likely that the growing understanding of T-cell-immunology in EGPA will lead to differentiated new treatment approaches.

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**References**


When ANCA were first described in the early 1980s [1], it rapidly became apparent that the presence of these antibodies was very useful diagnostically. A debate ensued that logically asked the question as to whether these antibodies were merely useful biomarkers, or whether they were in fact part of the pathogenic process and capable of inducing the pathological features seen in this disease. Various attempts at modelling the autoimmune reaction to the autoantigens myeloperoxidase (MPO) [4–9] and proteinase-3 (PR3) [10] followed, with the seminal studies of Xiao, Heeringa, Falk and Jennette [11] proving that, under certain circumstances, antibodies directed against MPO were sufficient to recapitulate the glomerular pathology seen in human MPO-ANCA vasculitis. Once the acute vasculitic pathology had been successfully modelled in this and related animal models, it opened the door to dissecting the biological components that were either necessary or not required for development of pathology, including neutrophils (essential) [12,13], T cells (variably essential depending on model) [12,14], B cells (variably dispensable depending on model) [12,14], Toll-like receptors (TLR2, 4, 9 exacerbate) [15–23], mast cells (attenuate) [18], tumour necrosis factor α [19,20] and the alternative complement pathway (essential) [21–23]. The latter was surprising, given that complement was not conventionally thought to be important in ANCA vasculitis, and has led directly to a clinical trial investigating the efficacy of an oral C5a receptor antagonist in affected patients, to date the only new therapeutic agent ever developed and tested for use in this disease (clinical trial ID NCT01363388). Thus, the last decade has seen an explosion of our knowledge in MPO-ANCA vasculitis, but not conventionally thought to be important in ANCA vasculitis, and has led directly to a clinical trial investigating the efficacy of an oral C5a receptor antagonist in affected patients, to date the only new therapeutic agent ever developed and tested for use in this disease (clinical trial ID NCT01363388). Thus, the last decade has seen an explosion of our knowledge in MPO-ANCA vasculitis, and has led directly to a clinical trial investigating the efficacy of an oral C5a receptor antagonist in affected patients, to date the only new therapeutic agent ever developed and tested for use in this disease (clinical trial ID NCT01363388).

In vivo modelling of proteinase-3-ANCA vasculitis

A natural extension of the antibody transfer techniques of Xiao et al. was to attempt the same in PR3 associated disease. Pfister et al. reported experiments describing the induction of PR3 antibodies in PR3/elastase−/− mice, with passive transfer of these antibodies to PR3 replete 129 Sv/Ev mice in a manner directly analogous to the MPO−/− approach [10]. The recipients did not develop the same pathological features of vasculitis, although a subtle increase in inflammation was observed in TNFα-exposed skin. Why did this strategy fail when it worked so dramatically for MPO immunity? Although PR3 is expressed on the surface of human neutrophils in association with CD177 [24,25], it is not detectable on the surface of unstimulated murine neutrophils, so there is no available antigen for the antibody to bind to. In addition, the PR3 molecule is only 68% homologous with its human homologue, whereas it is 86% identical in the case of myeloperoxidase, and PR3 has very different physico-chemical properties to MPO (isoelectric point 6.7 and 10 respectively). Finally, it is conceivable that PR3 autoimmunity is not actually a central component of the clinical syndrome Granulomatosis with polyangiitis (GPA, Wegener), that it is in fact an epi-phenomenon. However, the results of a recent genome wide association study investigating the