Meeting report

Highlights of the 2nd EUVAS Vasculitis Course

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The second Vasculitis Course organised by the European Vasculitis Society (EUVAS) was held in the splendid Corsini Palace, on the river Arno, in the heart of Florence, on April 19-21, 2018. The Directors of the course were Drs David Jayne and Domenico Prisco, and the chairmen of the organising committee Drs Giacomo Emmi, Carlo Salvarani and Augusto Vaglio. There were 500 participants, including rheumatologists, nephrologists, internists, clinical immunologists, pathologists and other specialists. The course was primarily meant to be an educational event, and was based on plenary lectures on the different aspects of systemic vasculitic syndromes, but it also aimed at discussing "what's new in vasculitis"; thus, it also included lectures on peculiar aspects of vasculitis in the so-called "Focus on" session. Finally, sessions dedicated to specific organ involvement in vasculitis and to clinical case discussion were also included.

Among the various vasculitides, the ones that were most dealt with were anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, Behçet's syndrome, large-vessel vasculitis and large vessel involvement in fibro-inflammatory diseases such as IgG4-related disease (IgG4-RD). The course was opened by three lectures on the pathogenesis of ANCA-associated vasculitis, large-vessel vasculitis and Behçet's syndrome, given respectively by Drs J. Charles Jennette, Jörg Goronzy and Ahmet Gül. Sessions dedicated to the different vasculitis syndromes followed. This meeting report will describe the main topics discussed during the meeting, especially those covered by the plenary lectures, with particular emphasis on newer aspects regarding pathogenesis, clinical phenotype, diagnosis and management of vasculitis syndromes.

ANCA-associated vasculitis

In his opening lecture, Dr. J. Charles Jennette (Chapel Hill, NC, USA) outlined the pathogenesis of ANCA-associated vasculitis, with particular emphasis on the work performed by his laboratory over the past three decades. After emphasising the complexity of the immune response involved in ANCA-associated vasculitis, Dr. Jennette described the animal models that recapitulate the pathology of ANCA-associated vasculitis, namely myeloperoxidase (MPO)-ANCA models. These mouse models proved the pathogenicity of MPO-ANCA Ig, and also contributed to understanding the role of T cells, which mainly participate in the chronic phase of the disease. The models also highlighted the crucial role of neutrophils, which are required for tissue damage, and of pro-inflammatory cytokines, which serve as amplifiers of the immune response (1). Among the mechanisms involved in the generation of ANCA-associated disease in mice, the activation of the alternative complement pathway is certainly crucial, as evidenced by the observation that mice knocked-out for factor B do not develop the disease; likewise, blockade of the C5a receptor prevents the development of vasculitic lesions (2).The alternative complement pathway is activated by yet unknown soluble factors released by primed neutrophils. These observations have rapidly been translated into clinical research: in a recent clinical trial, the use of the C5a inhibitor CCX168 avacopan proved effective in the treatment of ANCA-associated vasculitis, as later discussed by Dr David Jayne (3). Additional novel data reported by Dr Jennette showed the pathogenic importance of FcG receptors in the modulation of disease severity and phenotype: knocking out all the

activating FcG receptors abrogates the disease, but even more interestingly, if the inhibitory receptor FcGR3B is knocked out, the mice tend to develop more granulomatous disease. Therefore, the modulation of the FcGR-mediated innate immune response is able to condition the occurrence of vasculitic vs granulomatous lesions.

The role of genetic factors in the predisposition to and in the phenotypic modulation of ANCA-associated vasculitis was discussed by Dr Ken Smith (Cambridge, UK). Candidate-gene studies had already demonstrated the presence of genetic susceptibility to develop ANCA-associated vasculitis syndromes (4-6). However, a major contribution was definitely provided by genome-wide association studies (GWAS), performed in Europe by the European Vasculitis Genetics Consortium (7) and in the US by the Vasculitis Clinical Research Consortium (8). Granulomatosis with Polyangiitis (GPA) and microscopic polyangiitis (MPA) exhibited distinct genetic associations, the former with *HLA-DP, PRTN3* and *SERPINA1* variants, the latter mainly with *HLA-DQ* variants. Notably, these genetic associations were stronger with ANCA-specificities (PR3- *vs*. MPO-ANCA) than with the clinical syndromes (7), leading to the concept that it would probably be more appropriate to classify ANCA-associated vasculitis into anti-MPO and anti-PR3 vasculitis rather than into clinical syndromes such as GPA and MPA; this would not only have a sound biologic and genetic significance, but also clinical and prognostic implications, as demonstrated by several studies (9).

ANCA-associated vasculitis includes a wide range of histological lesions, which differ according to clinical syndromes, ANCA-specificities, disease stage, organs involved and other factors. This topic was discussed by Dr Ingeborg Bajema (Leiden, The Netherlands), who underlined the importance of accurate sampling of renal biopsies -which often show only focal lesions- and of clinico-pathological correlations. Notably, the classification of ANCA-associated glomerulonephritis developed by the Leiden group into focal, crescentic, sclerotic and mixed classes has important prognostic implications (10) and has been validated by subsequent studies: biopsies classified as "focal" portend an excellent renal prognosis, while "sclerotic" biopsies are associated with a poor renal survival; an intermediate prognosis is seen for mixed and crescentic classes, with some discrepancies among studies probably due to the different evaluation of crescentic lesions. Dr Bajema also underlined that the glomerulonephritis associated with MPA shows more chronic injury at the time of presentation than glomerulonephritis in patients with GPA, a difference that may be due to a delayed diagnosis in patients with MPA compared to patients with GPA (11), or to an intrinsic characteristic of MPA to develop more slowly progressive damage in some patients.

Differences in clinical phenotypes among ANCA-associated vasculitides were analysed by Dr Alfred Mahr (Paris, France). A striking difference in relapses was detected between PR3-ANCA+ and MPO-ANCA+ patients by different studies: these converged to the notion that PR3-ANCA+ patients are more prone to relapse, and that again this is independent of the clinical syndromes, since PR3-ANCA+ patients have higher relapse rates and shorter disease-free survival than MPO-ANCA+ patients regardless of whether the whole patient population or only MPA or GPA groups are considered (12). The presence of differences in outcomes between subgroups of ANCA-associated vasculitis patients was better explained by a cluster analysis performed on 673 patients who had been enrolled in EUVAS trials: a prognostic separation could be seen using clinical features only, but the differentiation was more marked when ANCA-specificities were also considered. This study ultimately identified five clusters, which were named "renal ANCA-vasculitis with PR3-ANCA" (40% of subjects), "renal ANCA-vasculitis without PR3-ANCA" (32%), "non-renal ANCA-vasculitis"(12%), "cardiovascular" (9%) and "gastrointestinal ANCA-vasculitis" (7%). The five clusters had distinct death and relapse rates (9). Interestingly, considering PR3-ANCA positive patients vs GPA patients seemed to better differentiate response to rituximab or cyclophosphamide-azathioprine in the RAVE trial (13).

It is important to underline that, although PR3-ANCA+ patients and MPO-ANCA+ patients are more frequent respectively in GPA and MPA, the differences between these categories (PR3-ANCA vs GPA and MPO-ANCA vs MPA) may be substantial. Also, PR3-ANCA positivity does not coincide with the occurrence of granulomatous lesions, since a number of PR3-ANCA-negative or MPO-ANCA+ patients also exhibit granulomatous disease. Therefore, the biological and clinical differences between PR3-ANCA and MPO ANCA-positive patients may go well beyond the clinical and histological classification of the disease.

The heterogeneity of the clinical phenotype of ANCA-associated vasculitis is exemplified by the differences between limited (usually to the head and upper airway tract) and generalised disease, particularly in GPA. Dr Raashid Luqmani (Oxford, UK) outlined the main features of limited GPA, which is characterised by a frequently granulomatous histology, severe local damage, high recurrence rates, frequent ANCA negativity, and a chronic-grumbling course that progresses into a full-blown systemic disease in only a few patients. Although the treatment approach for localised *versus* generalised forms may differ, with aggressive immunosuppression (and in some cases plasma exchange) usually reserved to the latter, the former anyway requires continued and tailored treatment and a careful long-term follow-up (14, 15). The BVAS and VDI scores, initially designed to evaluate disease activity and cumulative damage, can be used to assess disease extent and recently proved able to predict prognosis (16).

The last two lectures in the ANCA-associated vasculitis session focused on treatment and were given by Dr Kirsten de Groot (Offenbach, Germany) and Dr David Jayne (Cambridge, UK), who respectively discussed conventional and newer drugs. Dr De Groot outlined the

different therapeutic approaches based on disease extent, as summarised in the recent EULAR-EDTA recommendations (14, 15), and the many lessons learnt from randomised controlled trials: among the main take-home messages were the effectiveness of methotrexate in limited disease, although often followed by a high relapse rate; the comparable efficacy in inducing remission of pulse and oral cyclophosphamide (with the former being able to reduce the cumulative drug dose but also carrying a higher relapse risk), and the better response to rituximab than to cyclophosphamide in relapsing, PR3-ANCA+ patients. In addition to outlining these milestones of treatment, Dr De Groot also showed that new approaches combining low-dose cyclophosphamide and rituximab may be effective and have the potential to reduce relapses, although this has not yet been demonstrated in the setting of randomised controlled trials (17).

Among the newer therapeutic approaches discussed by Dr Jayne was plasma exchange (PEX), not because it is a new treatment but because it is being tested in a randomised trial, the PEXIVAS trial. The role of PEX in ANCA-associated vasculitis is in fact still controversial. It has been demonstrated that it improves renal recovery in patients with rapidly progressive ANCA-associated glomerulonephritis (18), but its role in patients with less severe renal disease or with other manifestations that currently prompt its use (*e.g.*, alveolar haemorrhage) is still unclear.

One of the most promising therapeutic approaches in ANCA-associated vasculitis is complement alternative pathway inhibition, particularly blocking the C5a receptor with the oral inhibitor avacopan. A recent industry-led trial tested conventional induction treatment (cyclophosphamide or rituximab) plus either high-dose steroids, low-dose steroids and avacopan, or avacopan without steroids. The avacopan arms induced a more rapid decrease in proteinuria and had positive effects also on health-related quality of life measures, a finding possibly related to the reduced (or absent) steroid therapy (3). This agent is currently being tested in a phase III trial.

Another drug that is under investigation is belimumab, a monoclonal antibody targeting BlyS, a survival factor for B cells. Preliminary experimental data show that combining belimumab and rituximab is particularly effective in depleting not only circulating but also tissue B cells, which often persist within the lesions when B-cell depletion is achieved with rituximab only. These observations laid the groundwork for a currently ongoing trial combining rituximab and belimumab for ANCA-associated vasculitis (COMBIVAS).

Eosinophilic granulomatosis with polyangiitis

The session on eosinophilic granulomatosis with polyangiitis (EGPA) was opened by a lecture on disease pathogenesis, given by Dr Augusto Vaglio (Parma, Italy). EGPA is a complex disease; genetic and (yet unclear) environmental factors contribute to its pathogenesis. Early studies on the genetics of EGPA demonstrated a strong association with *HLA-DRB* (4, 19) thus implying an antigen-driven pathogenesis which also involves CD4+ T cells. CD4+ T cells are plastic in EGPA, since they can differentiate into Th1, Th2 and Th17 cells, although the Th2 signature seems to be predominant (20). CD4+ T cells also boost eosinophil differentiation, and eosinophils themselves are able to promote Th2 cell expansion through the production of IL-25 (21). Tissue-resident cells such as endothelial and epithelial cells amplify the immune reaction in EGPA, since they are able to chemoattract eosinophils through the release of eotaxin-3 (22). Eosinophils are likely the key cells in inducing tissue damage in EGPA through the secretion of their granule proteins, and marked peripheral eosinophilia is a cardinal feature of EGPA at disease presentation. The humoral response is also dysregulated, with the production of ANCA in approximately 40% of the patients and with an increase in IgG4 responses (23, 24) ANCA probably mediate vasculitic lesions. B cells are also involved in the pathogenesis, as proven by the efficacy of rituximab treatment for induction and maintenance of EGPA (25, 26).

However, EGPA does not have a homogeneous phenotype: several studies identified distinct disease subsets mainly related to the ANCA status, with ANCA+ patients developing more frequently vasculitic lesions (*e.g.*, glomerulonephritis, neuropathy) and ANCA-negative patients more eosinophilic manifestations (*e.g.*, myocarditis). This clinical dichotomy probably recognises distinct pathogenic mechanisms and genetic determinants, as demonstrated by candidate-gene studies and by the ongoing EGPA GWAS (19, 27).

The clinical characteristics and major phenotypes of EGPA were discussed in detail by Dr Benjamin Terrier (Paris, France). Dr Terrier first underlined the difficulty in diagnosing or classifying EGPA; although the American College of Rheumatology 1990 criteria have commonly been used to classify EGPA, they are based on the assumption that a patient has vasculitis, which is often not the case for EGPA patients, who commonly lack evidence of vasculitic lesions. To overcome this problem, the recent MIRRA trial on mepolizumab for EGPA adopted a new set of criteria, which require the presence of asthma, hypereosinophilia, and at least two of the following items: histologic evidence of vasculitis or eosinophil-rich granulomatous infiltrates, cardiomyopathy, sino-nasal abnormalities, non-fixed lung infiltrates, purpura, glomerulonephritis, peripheral neuropathy, alveolar haemorrhage, and positive ANCA (28). Although these criteria have not been formally validated, they are widely accepted by most authors.

Dr Terrier also touched on different clinical manifestations of EGPA, and focused on cardiomyopathy, which is certainly one of the major causes of death. Cardiomyopathy mainly occurs in ANCA-negative EGPA, and consequently both ANCA-negativity and the presence of cardiac involvement are associated with a shorter survival (29). It is also important to acknowledge that, while clinically evident cardiac involvement is an important outcome predictor, subclinical cardiac lesions only

detected by cardiac magnetic resonance have uncertain prognostic significance. Finally, the importance of the differential diagnosis with other eosinophilic disorders was pointed out, particularly with eosinophilic lung diseases such as acute hypersensitivity pneumonia, chronic eosinophilic pneumonia, allergic broncho-pulmonary aspergillosis, parasitic, allergic and neoplastic diseases. Additionally, it must be recognised that some patients with a suspected diagnosis of EGPA but mainly presenting with asthma, eosinophilia and systemic symptoms may not actually fulfil the criteria for EGPA and are now classified as having hypereosinophilic asthma with systemic manifestations (HASM) (30).

Dr Terrier also gave a lecture on the treatment of EGPA, which is a rapidly evolving field. Until a few years ago, the therapeutic approach for EGPA was essentially based on the prognostic profile of the patients. The five factor score (FFS), including CNS, gastrointestinal, cardiac involvement, elevated creatinine and proteinuria, is the main prognostic score for EGPA; patients with a FFS=0 were treated initially with steroids alone, while patients with a FFS ≥1 were given induction therapy with cyclophosphamide and steroids. Newer agents have now become available; among them, mepolizumab and rituximab are supported by quite solid data. Mepolizumab, an anti-IL-5 monoclonal antibody licensed for the treatment of eosinophilic asthma, was initially tested for EGPA in pilot studies (31) and subsequently in the randomised controlled MIRRA trial (28), which compared mepolizumab (300 mg every 4 weeks) and placebo on top of standard therapy in patients with relapsing or refractory disease. The trial demonstrated that mepolizumab was superior in inducing and maintaining remission, although treatment withdrawal was followed by frequent relapses. Patients in the MIRRA trial were largely ANCA-negative and had a low frequency of vasculitic manifestations, therefore no conclusions could be drawn regarding the efficacy of mepolizumab on these disease features. Rituximab has also gained popularity in EGPA, as demonstrated by recent retrospective studies that showed its ability to induce and maintain remission (25, 26). In contrast with mepolizumab, rituximab proved particularly effective in ANCA-positive patients. Thus, the landscape of EGPA treatment is changing, and a shift from conventional to newer therapies is likely to occur, with the aim to achieve more sustained remission and spare steroids.

Behçet's syndrome

In his opening lecture, Dr Ahmet Gül (Istanbul, Turkey) discussed the main pathogenic mechanisms of Behçet's syndrome (BS). In addition to genetic and environmental factors, Dr Gül emphasised the immunological alterations underlying the disease. Many of the typical features of BS are related to the innate immune deviation, with increased levels of different cytokines, such as IL-1, IL-6, CXCL8 (IL-8), and TNFα. Neutrophils are the main inflammatory cells in BS, and almost all of the disease manifestations (*e.g.*, hypopyon uveitis, pathergy phenomenon, thrombosis) are due to non-specific neutrophilic hyperinflammatory responses (32, 33). Adaptive immunity also has a major role. In particular, a Th1 and Th17 polarisation has been described in BS (34, 35). As discussed by Dr Gül, the activation of immune responses could depend on antigen presentation to CD8+ T cells in the context of the class I molecule HLA-B51 (adaptive response). Moreover, HLA-B51 is able to interact with specific receptors on natural killer and γδ T cells, thus activating the innate response. Finally, folding antigen alterations could lead to unfolded protein response, typical of autoinflammation. Recently, it has been demonstrated that BS patients' sera are immunoreactive against neurofilament medium (NF-M). Interestingly, NF-M has a high structural homology with bacterial HSP-65, previously identified as the potential activator of lymphocytic responses via mimicry mechanisms (36).

Since its first description, the contribution of HLA-B51 has been confirmed in different ethnic groups and the distribution of this allele fits the geographical distribution of the disease. The two GWAS conducted on Turkish and Japanese populations also confirmed the significant contribution of the HLA-B region to the pathogenesis of the disease (37, 38). The imputation analysis of the GWAS also revealed a strong correlation between HLA-B51 and Endoplasmic Reticulum Aminopeptidase (ERAP)-1 (39). As outlined by Dr Gül, ERAP1 is crucial for digestive processes of cytoplasmic proteins. The release of proteins of non-optimal length can favour the unfolded protein response through HLA-B51, finally leading to autoinflammation.

The GWAS also showed non-HLA polymorphisms with biological significance, including IL-10, IL23R/IL12RB2, IL12 and STAT4. More recently, IL-1 polymorphisms have been demonstrated, with lower expression of IL-1α and higher expression of IL-1β (40). Moreover, association with rare autoinflammatory variants (TLR4, NOD2 and M694V) has been demonstrated (41). Dr Gül concluded his lecture showing some data on a newly described monogenic NF-kB-mediated autoinflammatory disease with BS-like manifestations, known as A20 haploinsufficiency. This recently described condition has mucocutaneous manifestations resembling those of BS, but different ocular symptoms and some autoimmune features (lupus-like manifestations).

Dr Haner Direskeneli (Istanbul, Turkey), discussed the more recent data on environmental factors triggering BS. A study by Dr Mahr's group described fatigue/stress and histamine-rich food as the most frequent triggers for BS-related oral ulcers (42). Interestingly, the replication of the same study on a Turkish population showed some differences, especially on mechanical hyper-reactivity mechanisms (dental treatment and tooth brushing) (unpublished data). Infections have long been studied in BS, and several direct and indirect mechanisms have been suggested. In particular, in BS patients oral health is impaired, also in the early phases of the disease (unpublished data).

Moving to microbiome, two main studies with controversial results have been mentioned by Dr Direskeneli. The first study on fecal microbiome showed a

significant reduction in bacterial biodiversity in BS patients compared to healthy controls (43). On the contrary, no changes in bacterial diversity were reported in a Japanese study, probably suggesting some differences related to ethnicity or geographical distribution (44). Notably, Consolandi and colleagues also showed a significant reduction in butyrate production, a short chain fatty acid able to control immune homeostasis (43).

BS can be considered as a model to dissect the mechanisms of thrombo-inflammation, and the vascular phenotype of BS is of particular interest since it represents a model of inflammation-induced thrombosis. This concept was outlined by Dr Giacomo Emmi (Firenze, Italy). In clinical practice, it is well known that immunosuppressants (rather than anticoagulants) are the treatment of choice for vascular involvement, namely thrombosis, in BS. However, only very few studies have been performed to elucidate the inflammatory nature of thrombosis in BS. Recently, it has been demonstrated that microparticles (MPs) are increased in BS patients compared to healthy controls; more importantly, MPs expressing tissue factor (a key molecule in the coagulation cascade) are more abundant in BS patients with vascular involvement than in those without thrombosis (45). As mentioned by Dr Gül in his opening lecture, neutrophils are the effector cells in BS. Notably, the correlation between neutrophils and fibrinogen abnormalities can help explain the mechanisms of thrombo-inflammation. Dr Emmi showed that in BS patients neutrophils are able to produce high amounts of reactive oxygen species (ROS), mainly through the NADPH oxidase complex. The increase in plasma oxidative stress markers leads to fibrinogen carbonylation, and in turn to a deep alteration of its secondary structure. Ultimately, this structural modification favours a markedly reduced fibrinogen plasmin-induced lysis (33). More recently, the same Italian group showed in a large retrospective study on 70 patients with vascular involvement the efficacy of immunosuppression for the treatment of venous thrombosis (46). Of note, the EULAR recommendations on the use of anti-TNFα for venous involvement in BS are mainly derived from the experience on the treatment of the arterial manifestations. The retrospective study presented by Dr Emmi showed that an adalimumab (ADA)-based regimen (*i.e.*, ADA alone or ADA plus a conventional DMARD) was more effective and rapid in inducing vascular responses than DMARDs alone, also allowing to reduce corticosteroid exposure. As also discussed by Dr Gulen Hatemi, interferon (IFN)-α also seems to be effective on venous involvement, with a very low rate of recurrence in a yet unpublished Turkish study. Altogether, these findings confirm in the clinical practice the peculiar and unique inflammatory nature of thrombosis in BS.

As pointed out by Dr Emire Seyahi (Istanbul, Turkey), BS has different clinical phenotypes. Among these, the acne/arthritis cluster (mainly in the Turkish population) together with the vascular and gastrointestinal ones, suggest that BS is a syndrome rather than one single entity. Therefore, its treatment must also be individualised, mainly according to gender, age, kind and severity of the organ involvement, as underlined by Dr Gulen Hatemi (Istanbul, Turkey). Dr Hatemi started the last lecture of the session dedicated to BS showing for the first time the recently published updated EULAR recommendations for the treatment of BS-related manifestations (47). Dr Hatemi initially discussed ocular involvement, one of the most important in BS. Patients with refractory isolated anterior uveitis, especially men, should be treated with azathioprine to avoid recurrences. Biologic agents should be reserved to patients with negative ocular prognostic factors (*e.g.*, male gender, posterior involvement, frequent attacks). Despite infliximab (IFX) seems to have a more rapid action compared to IFN-α, patients on anti-TNFα treatment experience a less durable remission after discontinuation and a higher steroid exposure. On the other hand, IFX and IFN-α are associated with comparable remission rates and safety profile. More recently, ADA also proved to be highly effective in a multicentre retrospective study on 40 patients (48). Dr Hatemi presented data on anti-IL1 treatment for BS-related uveitis. Anakinra (ANA) and canakinumab (CANA) recently demonstrated in a retrospective multicentre study to significantly reduce the number of ocular attacks. However, compared to ADA, anti-IL1 did not affect visual acuity. In conclusion, Dr Hatemi stated that anti-IL-1 agents are useful treatments for ocular involvement in BS, but with a lower effect size than anti-TNF-α.

The use of anticoagulants is still a matter of debate in BS. As already underlined, retrospective studies have suggested that immunosuppressants are able to reduce vascular recurrences (49, 50). Dr Hatemi also underlined the concept that since venous thrombosis usually precedes aneurysm formation, anticoagulation should be started only after the arterial involvement has been ruled out.

For the management of parenchymal involvement of the CNS in BS, as for its gastrointestinal manifestations, few solid data are available. In both CNS and gastrointestinal lesions, TNFα inhibitors can be useful especially for refractory patients. Small case series have also suggested the use of tocilizumab in refractory CNS (51).

The last part of Dr Hatemi's lecture focused on mucocutaneous involvement. Oral and genital ulcers, as well as erythema nodosum, are usually treated with topical drugs or colchicine; for selected refractory cases, azathioprine or biologicals (anti-TNFα and IFN-α) can be used. Conversely, tocilizumab has recently been reported to induce flares of mucocutaneous manifestations, so to date its use in this type of organ involvement remains controversial. Otherwise, a recent prospective study with ANA showed some benefit, especially doubling the dosage (200 mg/day) (52). A partial beneficial effect on oral ulcers has also been demonstrated in a small prospective study with ustekinumab (53). Lastly, Dr Hatemi showed the data of the phase II trial on the phosphodiesterase (PDE)-4 inhibitor apremilast (54). Apremilast reduced the number oral ulcers and related pain, with a response rate (considered as complete plus partial) of about 90%. The recently

completed phase III trial has substantially confirmed the data on the effectiveness of apremilast (unpublished).
Overall, looking at Dr Hatemi's lecture, we can conclude that azathioprine is the drug of choice as first line to treat all the types of organ involvement in BS. Among the biologicals, anti-TNFα and IFN-α are the most effective. However, also anti-IL1 agents and tocilizumab could be effective for specific lesions. Finally, new drugs (as apremilast) could be useful in the near future for the treatment of refractory mucocutaneous manifestations.

Large-vessel vasculitis

Large-vessel vasculitis (LVV) comprises a spectrum of diseases primarily causing inflammation of the aorta and its main branches as well as other medium-sized and large arteries; prototypical examples of LVV are giant cell arteritis (GCA) and Takayasu arteritis (TA) which recognise common pathogenic mechanisms that lead to granulomatous inflammation of the media and adventitia. Dr Jörg Goronzy (Stanford, USA) gave one of the opening lectures focusing on recent developments in the pathogenesis of LVV, with particular reference to the work done by his group over the past few years. Among the most recent advances in LVV pathogenesis is the comprehension of the critical role of adventitial microvascular endothelial cells, which have immunoregulatory functions by up-regulating the expression of the Notch ligand Jagged1. Vascular endothelial growth factor (VEGF) induces Jagged1 expression, allowing microvascular endothelial cells to regulate effector T cell induction via the Notch-mTORC1 pathway. In an *in vivo* model of LVV, exogenous VEGF functioned as an effective amplifier to recruit and activate vasculitis-inducing T cells (55).
Within the vascular wall, the crosstalk between vascular dendritic cells and effector T cells is also essential for the development of vasculitis; one critical mechanism is centred on the regulation of the immune check-point inhibitor PD-1 (expressed on T cells) and its ligand PD-L1 (expressed on dendritic cells). In GCA arteries, vascular dendritic cells are unable to up-regulate PD-L1: this facilitates vascular invasion by PD-1+ T cells. In an *in vivo* model of GCA, vessel-invading PD-1+ T cells secreted large amounts of cytokines such as IFNγ, IL-17 and IL-21, which play a critical role in GCA pathogenesis, and also promoted neoangiogenesis and intimal hyperplasia (56). The results of these recent works suggest that manipulating the interaction between microvascular endothelial cells and T cells as well as the PD1-PDL1 co-inhibitory pathway may open new avenues for the treatment of LVV.
LVV has a complex and heterogeneous genetic background; this topic was discussed by Dr Javier Martín (Granada, Spain). Dr Martín illustrated the results of recent large-scale genetic studies performed using GWAS- and Immunochip-based approaches, which led to the discovery of interesting genetic associations with both GCA and TA in addition to confirming previous HLA associations. The first Immunochip analysis performed on >1,600 GCA patients revealed associations with polymorphisms of *PTPN22*, a common denominator of autoimmune diseases, and *LRRC32*, which is involved in regulatory T cell functions (57). A more recent GWAS, performed on >2,100 GCA patients, identified associations with gene variants of *PLG* (plasminogen) and *P4HA2*, both involved in vascular remodelling and angiogenesis (58).
While GCA is mainly associated with HLA class II variants, TA is essentially an HLA class I-associated disease. This distinction was also confirmed by a meta-Immunochip study, which was based on a meta-analysis of the previous Immunochip studies in GCA and TA. Despite these differences, GCA and TA also showed a shared genetic association with IL12, an interesting finding especially in light of newer therapies that aim to block the IL-12/IL-23 pathway in LVV (59, 60).
The pathology of GCA was reviewed by Dr Alberto Cavazza (Reggio Emilia, Italy), who focused on peculiar abnormalities that can be detected on temporal artery biopsies in GCA patients. He first discussed vasa vasorum vasculitis as well as vasculitis of periadventitial small vessels, which can be in a few cases the only abnormal finding: these abnormalities are associated in some studies with a lower frequency of cranial and systemic symptoms (although not with a lower frequency of visual complications); additionally, vasa vasorum and periadventitial vessel vasculitis should raise suspicion of an underlying systemic disease (*e.g.*, ANCA-associated vasculitis) (61). Subsequently, Dr Cavazza discussed more common findings in GCA, such as transmural inflammation and granulomas, and also emphasised possible clinico-pathological correlations: interestingly, cranial ischaemic events appear to be associated with giant cells and laminar necrosis, while visual symptoms with vascular calcifications and laminar necrosis (62). Some temporal artery biopsies show no inflammation, and some authors have proposed that histological findings that evoke a "healed" arteritis should also be taken into account for a diagnosis of GCA. Dr Cavazza's experience, based on the review of a large cohort of temporal artery biopsies, was not in line with this view, suggesting that a diagnosis of GCA should only be made when inflammation is detectable.
Dr Peter Merkel (Philadelphia, USA) provided an overview of the complex spectrum of LVV, which is not limited to GCA and TA but also includes a wide array of conditions that can cause inflammation of large vessels (*e.g.*, IgG4-related disease, BS, relapsing polychondritis) as well as primary inflammatory diseases of the aorta and its main branches that cannot be classified as GCA or TA and that lack extravascular manifestations (*e.g.*, isolated ascending aortitis). Additionally, within well-defined LVV syndromes such as GCA, patterns with no cranial involvement but with sole evidence of large-vessel inflammation on imaging studies can be recognised (63). Therefore, the spectrum is wide and complex, and probably only the advent of more sophisticated imaging techniques and genetic or molecular biomarkers will allow a more accurate definition of LVV subsets.
Polymyalgia rheumatica (PMR) is also within the spectrum of LVV, being present in up to 40% of patients with GCA

and sometimes occurring as an isolated entity. Imaging studies have shown that up to one-third of PMR patients have subclinical large-vessel inflammation at presentation (64). This finding further supports the hypothesis that different stages and extent of large-vessel inflammation occur in these syndromes, and that probably regulatory mechanisms that prevent clinically overt vasculitis are in place in PMR while they are dysregulated in GCA. This topic was discussed by Dr Christian Dejaco (Graz, Austria), who also highlighted conventional and new therapeutic approaches for PMR, the latter also including tocilizumab (65), which is being tested in several trials.

The true extension of vascular inflammation and the actual risk of large-vessel complications in LVV have been better appreciated in the last few years thanks to the wider use of imaging techniques such as CT-angiography, MR-angiography, and FDG-PET. Dr Nicolò Pipitone (Reggio Emilia, Italy) gave a lecture on this topic, and provided major take-home messages: imaging studies are useful to document temporal artery inflammation in GCA and essential to show large-vessel inflammation in early LVV. Ultrasound, CT and MR are able to show early vasculitic lesions, characterised by inflammatory vessel wall alterations with initial sparing of the vessel lumen. Ultrasound, CT-angiography, MR-angiography and conventional angiography are able to show and to monitor LVV complications such as arterial stenosis, occlusion and aneurysm formation. A better standardisation of the scoring methods used to interpret PET scans is needed. In clinical practice, PET is useful to diagnose untreated individuals with suspected large-vessel vasculitis and contributes to identify patients at risk for vascular complications (66).

The LVV session closed with the lecture given by Dr Carlo Salvarani (Reggio Emilia, Italy) on the treatment of LVV. Dr Salvarani outlined conventional therapies for GCA, with a particular focus on the findings obtained by randomised controlled trials: these trials investigated the efficacy and safety of several immunosuppressants such as methotrexate, azathioprine, and TNF inhibitors, none of which clearly demonstrated significant benefit (67). The revolution came very recently with the introduction of the anti-IL-6 monoclonal antibody tocilizumab, which was tested in two randomised trials (68, 69). Tocilizumab proved efficacious as compared with placebo in inducing disease remission and preventing relapses, and also allowed substantial reduction in steroid exposure. Open questions on the use of tocilizumab remain: first, can IL-6 inhibition have deleterious effects on angiogenesis and ultimately cause late ischaemic events? Second, which patients with GCA should be treated, *i.e.* only those at high risk of steroid-related complications? Third, how long should GCA patients receive tocilizumab for? Dr Salvarani also reviewed other current and future options for GCA, such as ustekinumab, which targets IL-12/23 p40; this was reported, with encouraging results, in a small GCA trial (60). Also, JAK-STAT inhibitors are being tested, based on the experimental observation that they can halt innate and adaptive immune responses in the vascular wall in mouse models of GCA (70).

The positive experience with tocilizumab in GCA was translated in TA; a very recent phase III trial suggested that tocilizumab may be effective in reducing time to relapse in TA patients (71), thus opening new frontiers for the treatment of this difficult-to-manage condition.

Large vessel involvement in fibro-inflammatory diseases

Fibro-inflammatory diseases (FID) encompass a wide variety of pathological conditions characterised by chronic (lympho-monocytic and plasmacytic) inflammation and exuberant fibrosis. These diseases include chronic pancreatitis and cholangitis, chronic periaortitis, sialoadenitis, mediastinal fibrosis and others. These lesions can be classified as IgG4-related or –unrelated, depending on some histological features and the extent of the tissue IgG4-response. Dr Augusto Vaglio (Parma, Italy) discussed vascular involvement in FID, which is usually under the form of aortitis or periaortitis. These two conditions essentially differ on the basis of the thickness of the periaortic fibro-inflammatory response, which is particularly marked in periaortitis, where it can cause compression of adjacent structures such as the ureters or the inferior vena cava (72). Periaortitis is a common manifestation of FID, and can be either localised to the abdominal aorta or involve the thoracic aorta and the origin of epiaortic arteries (73). Different factors such as genetic determinants and environmental factors (*e.g.*, asbestos exposure, smoking) (74) contribute to its pathogenesis, while the immune response involves the participation of different cell types- particularly T cells, macrophages, B cells and plasma cells (75), and the secretion of pro-inflammatory cytokines such as IL-6 (76).

IgG4-related disease and IgG4-unrelated FID are often difficult to differentiate, and the histological and immunohistochemical criteria that are currently used do not allow, in most cases, a clear-cut distinction between these forms (77). This issue was discussed by Dr Domenico Corradi (Parma, Italy), who showed that these lesions can be incorporated in a single disease spectrum, and that histological features that are commonly considered as hallmarks of IgG4-related disease, namely storiform fibrosis and obliterative phlebitis, are not uniformly present across the pathological specimens and are often difficult to detect. In addition, the histological characterisation of FID lesions may vary depending on disease stages (more inflammatory in the early phases, more fibrotic in the late ones) and on the sampling techniques.

Dr Nicolas Schleinitz (Marseille, France) concluded the session on FID with an overview on treatment; Dr Schleinitz critically analysed which conditions do need treatment, and which only warrant careful follow-up. He emphasised the steroid-sensitivity of most IgG4-related conditions, and also mentioned that rituximab can be an effective treatment option for both newly diagnosed and relapsing disease. He also proposed that systematic rituximab infusions can induce a longer relapse-free survival, although treatment-related toxicity is not negligible (78).

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