Actualities in the Treatment of Systemic Vasculitis

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Remarkable progress in understanding the pathogenetic mechanisms of systemic vasculitis have been made in the past few years that have lead to the development of new therapeutic alternatives that expanded the options for patient management. However, optimal treatment of vasculitic syndromes is still debated. Controversies remain regarding the most effective regimens with minimum adverse effects. Lack of disease control and therapeutic toxicities of standard regimens based on glucocorticoids and cytotoxic agents remain major problems.

EUVAS (*European Vasculitis Study Group*) is a network organization with participation from 16 European countries aiming to harmonize and optimize current therapies and to establish a consensus approach for the treatment of vasculitis, through evidence-based strategies derived from a series of multicenter randomized controlled trials. The project started with the activities of the European Community Systemic Vasculitis Clinical Trials Study Group (ECSYSVAS-TRIAL). Its main objective included the design and standardization of disease scoring and data collection methodology for future therapeutic trials in ANCA-associated systemic vasculitis. The members of this organization have regular meetings twice annually, for informed discussions and consensus decisions based on preliminary results of the clinical trials. An outline of the studies intiated and conducted by EUVAS is presented in table 1.

Table 1: The activity of EUVAS

EUVAS Study	Aims of the study	Comments
CYCAZAREM	***Cyc*lophosphamide** versus ***Aza*thioprine** for ***rem*ission in generalised vasculitis	153 patients with Wegener and microscopic poli-angiitis (1)
MEPEX	***Me***thyl ***p***rednisolone versus **plasma *ex*change** for severe renal vasculitis	Preliminary results (2003): there is a benefit in favor of plasma exchange for the primary end-point of renal independence at three months.
NORAM	**Methotrexate** versus **cyclophosphamide** for 'early systemic' disease	No difference in induction of remission after 6 months.
CYCLOPS	Daily oral versus pulse cyclophosphamide for renal vasculitis	Recruitment completed
SOLUTION	Anti-thymocyte globulin for refractory vasculitis	Recruitment completed
REMAIN	Long-term low dose immunosuppression versus treatment withdrawal for renal vasculitis	Still actively recruiting
IMPROVE	MMF versus azathioprine for remission therapy in renal vasculitis	Still actively recruiting
CHUSPAN	Evaluation of different protocols for groups with good and poor prognostic factors in Churg-Strauss syndrome and polyarteritis	
ACTIVE	Infliximab (monoclonal antibody anti-TNF-alpha) in acute and sever forms of vasculitis, associated with conventional treatment	Still actively recruiting
MUPIBAC	Placebo-controlled trial of nasal mupirocin for the prevention of relapse in Wegener's granulomatosis	Recruitment suspended due to problems with the supply of the trial ointment. The protocol is presently being redesigned.

Severity scores

Detailed clinical assessment (severity of disease, activity and scarring) is very important for designing treatment requirements of an individual patient with vasculitis. Recording disease activity and recognition of chronic damage allow the rational use of a potentially toxic therapy. There are different assessment scores currently in use, based on clinical, radiological and laboratory assessment: *ELK score* (ear/nose/throat-lung-kidney) (2). *The Groningen Index* (3), *The Vasculitis activity index* (4), *The Birmingham Vasculits activity score* (BVAS) (5). The usefulness of some of these scores was evaluated by several clinical and therapeutical trials (6). Keller et al. (6) established the *Disease Extent Index-DEI (table 2),* a reproducible score with a good prog-

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nostic value: a DEI score >7 was associated with an unfavorable evolution and possible lack of response to immunosuppressive therapy.

Table 2 DEI (Disease extent index) - after Keller et al.[6]

Affected organ	*Score*	Standard diagnosis
Upper respiratory tract	2	*Clinical assessment, MRI, sinuscopy*
Lung	2	Chest radiograph, CT, bronhoscopy, bronchoalveolar lavage
Eyes	2	Clinical assessment, cranial MRI
Kidneys	2	Urine analysis, serum creatinine, abdominal ultrasound
Heart	2	ECG, chest radiograph, echocardiogram, myocardial scintigram, coronary angiogram
Gastro-intestinal tract	2	Abdominal ultrasound, endoscopy
Skin	2	Clinical assessment, skin biopsy
Peripheric nervous system	2	Neurological assessment, EMG, nerve biopsy
Central nervous system	2	Neurological assessment, lumbar puncture, cranial MRI
Rheumatic complaints	2	Radiographs, ultrasound, bone scan, EMG, MRI, muscle biopsy
Constitutional symptoms	1	

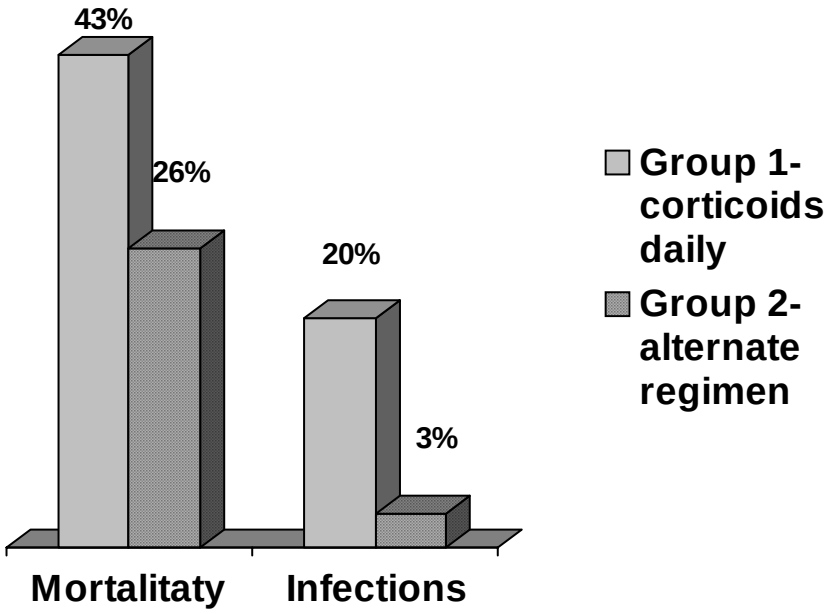
Daily corticotherapy or alternate day regimen?

The use of alternate day glucocorticoids tapering regimen after remission of vasculitis disease is an important strategy to minimize the serious side effects of these drugs. This was illustrated by a multicenter trial (7): the overall mortality and the rate of infectious complications were statistically significant greater in the group treated by corticoids daily (group 1) versus alternate regimen (group 2).

Daily oral or intermittent intravenous cyclophosphamide?

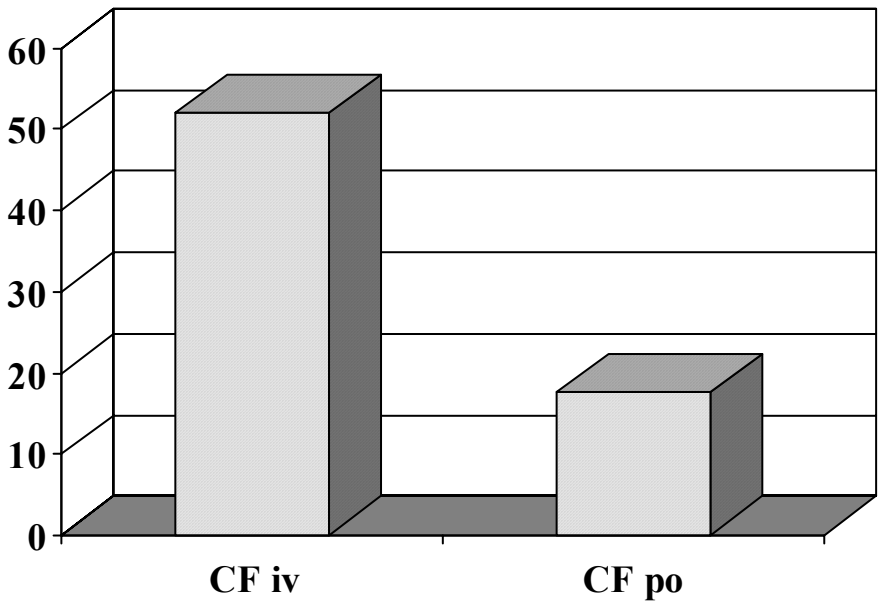
The use of intermittent intravenous pulses of cyclophosphamide has been investigated as one possible therapeutic alternative to daily cyclophosphamide. The EUVAS study CYCLOPS compares a) the efficacy in the induction phase, b) maintenance of remission and c) the adverse effects of these two forms of therapy in patients with renal vasculitis.

Figure 1. Comparative study of mortality and infectious complications in patients treated with corticoids daily versus alternate regimen- after Guillevin, 1997 (7)



The preliminary results were communicated by Guillevin, the French co-ordinator of the EUVAS group: intermittent intravenous cyclophosphamide was associated with fewer side effects, particularly cancer of the bladder and gonadal toxicity, but also with a greater relapse rate in patients with Wegener's granulomatosis when compared with oral regimen (Figure 2) (7). Several other studies in patients with minor forms of vasculitis found no difference in mortality, relapse rate and efficacy of these two forms of therapy, but more adverse effects in patients receiving cyclophosphamide orally (8,9).

Figure 2. The risk of relapse of WG: cyclophosphamide iv versus po (after Guillevin (7))



In conclusion: although controversies still remain, the majority of authors consider that intermittent pulse therapy with cyclophosphamide is associated with a higher likelihood of relapse and, for this reason, could be inadequate in patients with systemic aggressive vasculitis (10).

How long should we continue the alkilating agents?

The evolution of the patients with systemic vasculitis can be favorable if the immunosuppressive therapy is initiated before the occurrence of irreversible scarring lesions. The important toxic effects of cyclophosphamide makes the duration of treatment with this drug an important issue. CYCAZAREM (CYClophosphamide or AZathioprine As a REMission therapy for systemic vasculitis) is the first EUVAS study already finished (1). This study found that the remission was obtained in 93% of the 156 patients who received cyclophosphamide po and glucocorticoids. There was no significant difference at 18 months in the relapse rate between patients who received maintenance therapy with azathioprine after the induction of remission and those treated with cyclophosphamide for 12 months and then switched to azathioprine. The adverse effects of these two immunosuppressive regimens were similar, probably because of the short duration of the trial (it is well known that many toxic effects of cyclophosphamide are not manifested until years after the initiation of therapy).

In conclusion: there is evidence that azathioprinemay be substituted to cyclophosphamide for maintenance therapy without an increase in the rate of relapse throughout a period of 18 months.

Other therapeutic agents

Methotrexate

Methotrexate has been investigated as a less toxic alternative to cyclophosphamide for the treatement of moderate forms of vasculitis (without life-threatening complications such as pulmonary hemorrhage, renal insufficiency requiring dialysis). The remission rate was acceptable (79%) and the relapses (58%) appeared in the majority of cases after the reduction or discontinuation of methotrexate (11). The preliminary results of the NORAM trial (methotrexate versus cyclophosphamide for 'early systemic' disease) showed no difference in the remission rate between the two groups.

Recent data suggests that methotrexate can be use effectively to maintain remission in patients initially treated by corticosteroids and cyclophosphamide. This immunosuppressive protocol is attractive because it combines the effi-

cacy of cyclophosphamide (used with minimal risk for a limited period) together with methotrexate, a drug with a more favorable toxicity profile and a simple weekly administratiion. In a report by Langford (12), in 31 patients treated with this immunosuppressive protocol, the relapse rate at 2 years was only 16%.
In conclusion: methotrexate is a less toxic and efficient alternative to cyclophosphamide for induction of remission in patients with not immediately life-threatening vasculitis and for maintenance of remission in patients initially treated with glucocorticoids and cyclophosphamide.

Trimethoprim/sulfamethoxazole
The use of trimethoprim/sulfamethoxazole has been investigated for its beneficial role in preventing relapses in Wegener's granulomatosis, probably by reducing the nasal portage of staphylococci. It seems that this drug reduces only the recurrence of upper airway disease and not the relapses in other organs (13). However, this drug has an incontestable beneficial effect when administered in a low dose in patients treated with aggressive immunosuppressive regimens: prophylaxis of opportunistic infections with Pneumocystis and Nocardia.

New therapeutic strategies in vasculits
Recent research on the pathogenesis of vasculits has made significant progress in understanding the mechanism of the inflammatory process. This has resulted in the development of more selective drugs, acting at different specific targets while leaving host defense intact, less toxic and theoretically effective in patients with vasculits. An overview of these new strategies is presented in Table 3.

Conclusion
Although the standard regimen of glucocorticoids and cytotoxic agents has a high response rate in induction of remission in systemic vasculitis, his toxic profile remains a major problem. Recent progress in understanding the complicated pathogenic mechanism of inflammation in vasculitis permitted the development of new attractive therapies with exquisite specificity. These promising therapeutic possibilities need, however, to be further investigated in large, controlled clinical trials.

Table 3. New therapies for systemic vasculitis

	Drug	Mechanism	Comments
New immunosuppressive agents	**Mycophenolate mofetil (MMF)**	Selectively inhibits IMPDH	Effective in reducing perivascular inflammation in an animal model of lupus (14) Effective in maintenance of remission in patients with Wegener granulomatosis and microscopic poliangiitis (15)
	Leflunomide	Blocks pyrimidine synthesis and inhibits the TNF-dependent transcription factor NF-κB	Alternative to cyclophosphamide for remission maintenance in patients with ANCA positive vasculitis (16)
	Deoxyspergualin	Inhibits the activation NF-κB	Beneficial effect in five patients with prolipherative glomerulonephritis (17)
	Etoposide	Inhibitor of mitosis	Efficient in Wegener's granulomatosis and microscopic poliangiitis, resistant to the traditional regimen (18)

	Drug	Mechanism	Comments
Antilymphocytic therapies	**Monoclonal antibodies anti- CD 52 (CAMPATH-1H) and anti-CD4**	Depletion of CD52+ and CD4+ lymphocytes	Effective and few side effects in patients with systemic vasculitis resistant to conventional agents (19)
	Daclizumab	Monoclonal antibody anti Tac (anti IL2-R)	Investigation of the possible role of daclizumab in the prevention of relapses in Wegener's granulomatosis- *The National Institute of Allergy and Infectious Diseases, 2002*
	Monoclonal antibodies modulators of lymphocyte function	Block the interaction of T cells with antigen presenting cells	Beneficial effects in patients with psoriasis (20)
Anti-monocytes and neutrophils therapies	**Monoclonal antibodies anti-monocytes and neutrophils**	Block the adhesion molecule CD18	Beneficial effects in 5 patients with severe vasculitis (21)
Cytokine directed therapies	**Etarnecept**	Inhibition of TNF	Investigation of the possible role of Etarnecept in the reduction of the corticoids' dose in maintenance remission in Wegener's granulomatosis- *The National Institute of Allergy and Infectious Diseases*, 2002
	IFN-α	Reduction of circulating eosinophils	Beneficial effects in 4 patients with Churg Strauss syndrome (22)
Antibody removal therapies	**Immunoglobulin intravenous**	Block the receptors Fc, antibodies anti-citokines or anti-MHC	Effective in the short term in systemic vasculitis (23)
	Plasmapheresis	Removal of antibody	Efficacy in severe vasculitis with severe renal involvement (24)
Complement inhibition and endothelial cell regulation	Nafamostat mesilate	Inhibits the complement activation	Possible anti-inflammatory role
	Troglitazone	Inhibits the expression of adhesion molecules on endothelial cells	Possible anti-inflammatory role

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