Chapter 9

Treatment of ANCA-Negative Small Vessel Vasculitis

Christina G. Katsiari, Theodora Simopoulou and Lazaros I. Sakkas

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/54272

1. Introduction

Small vessels refer to arterioles, capillaries and venules. According to an international consensus conference, small vessel vasculitides include, ANCA-associated vasculitis (granulomatosis with polyangitis [Wegener's], Churg-Strauss syndrome, microscopic polyangiitis), cryoglobulinaemic vasculitis, Henoch-Scholein purpura, and cutaneous leukocytoclastic angiitis [1].

2. ANCA-associated vasculitis

2.1. Cryoglobulinaemic vasculitis

Cryoglobulinaemia refers to circulating cryoglobulins. Cryoglobulins are immunoglobulins, which precipitate in temperatures below 37°C and dissolve upon rewarming [2]. Cryoglobulinaemia is classified in 3 types based on clonality and immunoglobulin class. In particular, type I consists of monoclonal IgM or IgG immunoglobulin, type II is a mixture of monoclonal IgM and polyclonal IgG, while type III is a mixture of polyclonal IgM and IgG. Type II and III are also called "mixed", since both contain a mixture of IgM and IgG immunoglobulins [3]. The IgM component of type II cryoglobulins has rheumatoid factor activity (can bind to the Fc portion of IgG). All 3 types of cryoglobulinaemia may or may not result from an underlying disorder. In the absence of an identifiable cause cryoglobulinaemia is characterized as "essential".

Circulating cryoglobulins induce damage through 2 mechanisms: type I monoclonal IgM cryoglobulins, due to the large size of IgM and their high concentration levels – usually as-

sociated with Waldenström disease– result in hyperviscosity-induced vascular damage. On the other hand, type II and III mixed cryoglobulins in combination with complement components form immune complexes, which deposit in capillaries and small arterioles leading to vascular inflammation [3]. Patients with symptomatic mixed cryoglobulinaemic vasculitis typically display low serum levels of complement C4, reflecting complement consumption via the classical, immune complexed-mediated activation pathway. Palpable purpura represents a typical clinical manifestation. Skin biopsy reveals small vessel leukocytoclastic vasculitis namely inflammation and destruction of the vessel wall along with polymorphonuclear leukocyte nuclear debris. Involvement of internal organs, most commonly peripheral nerves, kidneys and joints will dictate prognosis and treatment decisions. Clinical and laboratory features of cryoglobulinaemia are summarized in Table1.

Treatment of mixed cryoglobulinaemic syndrome depends essentially on two parameters: First the type and severity of manifestations and second the underlying disease. It is apparent that the identification and treatment of the underlying cause is of paramount importance. Mixed cryoglobulinaemic syndrome is typically divided as hepatitis virus C (HCV) – related or not.

<table>
<tr><td colspan="6">CRYOGLOBULINAEMIA</td></tr>
<tr><td colspan="2">TYPE I
monoclonal
IgM or IgG</td><td colspan="2">TYPE II
monoclonal IgM + polyclonal IgG</td><td colspan="2">TYPE III
polyclonal IgM
+ polyclonal IgG</td></tr>
<tr><td>Essential</td><td>Secondary</td><td>Essential</td><td>Secondary</td><td>Essential</td><td>Secondary</td></tr>
<tr><td></td><td>Waldenström
Myeloma
Lymphoma</td><td></td><td>HCV
Myeloma
Lymphoma
Autoimmune
diseases</td><td></td><td>Autoimmune diseases
Chronic Inflammatory
diseases</td></tr>
<tr><td colspan="2">HYPER – VISCOSITY
Raynaud’s
Digital ischemia
Hyperviscosity syndrome</td><td colspan="4">CRYOGLOBULINAEMIC VASCULITIS
Purpura, Arthritis, Raynaud’s,
Renal disease, Neuropathy</td></tr>
<tr><td colspan="6">CLINICAL SYNDROME</td></tr>
</table>

Table 1. Clinical and laboratory characteristics of cryoglobulinaemia.

2.2. Treatment of HCV related cryoglobulinaemic vasculitis

2.2.1. Aiming the virus: Treatment of chronic HCV

The majority of cases with cryoglobulinaemia are considered to be induced by HCV. Evidence of HCV infection is usually displayed by serum antibodies against the virus or presence of HCV-RNA. It should be noted however that false negative results do occur. If

http://dx.doi.org/10.5772/54272

suspicion of HCV infection is strong further examination of the cryoprecipitate, where both antibodies and RNA are concentrated, should be performed. Management of patients in this category should take place in collaboration with a hepatologist

The role of interferon alpha (INFα) in the treatment of cryoglobulinaemic vasculitis has been examined approximately 2 decades ago. In an early study, among 53 patients with HCV – related cryoglobulinaemic vasculitis, only patients who displayed a drop in the virus RNA levels showed clinical improvement. Reduction of RNA levels was restricted to patients who received INFα in addition to conventional treatment [4]. Moreover, viremia, cryoglobulinaemia and clinical symptoms returned following INFα cessation. Apart from INFα therapeutic potential, this as well as similar studies showed that clinical response parallels the levels of viremia.

Addition of the broad spectrum anti-viral agent rivabirin proved to add therapeutic benefit to INFα monotherapy [5, 6]. More recently, PEGylated INFα combined with ribavirin was shown to have superior efficacy compared to non-pegylated INFα / ribavirin combination [7-9]. PEGylation is a process where polyethylene molecules (PEG) are covalently attached to, in this case, INFα producing a molecule with prolonged pharmacokinetics. A recent update of recommendations by the American Association for the Study of Liver Diseases is shown in Table 2 [10].

INFα (SC per week)	**plus**	Ribavirin (orally per day)
180 μg PEG-INFα-2a	+	BW<75kg: 1000mg, BW"/>75kg: 1200mg
	or	
1 – 5 μg PEG-INFα-2b	+	BW<65kg: 800mg, BW=65-85kg: 1000mg, BW=85-105kg: 1200mg BW"/>105kg: 1400mg

SC: subcutaneous, PEG-INFα: PEGylated interferon alpha, BW: body weight

Table 2. Antiviral combination treatment in HCV-related cryoglobulinaemic vasculitis

There are no definite guidelines regarding duration of treatment. Treatment of HCV infection is recommended to last from 24 weeks (for virus genotypes 2 and 3) to 48 weeks (genotypes 1 and 4). The rational behind this recommendation lies on the observation that if viral response has not been achieved within this time frame, it is highly unlikely that prolongation of treatment will lead to substantial and sustained viral response [10]. However, in the case of cryoglobulinaemic vasculitis accompanying HCV infection, a less strict approach is endorsed, where besides viral levels, clinical and immunologic features are also taken into account [7, 11]. Prolongation of antiviral therapies may be appropriate in a subset of patients who display clinical benefit and no drug intolerance [3].

2.2.2. Downregulation of cryoglobulins: Rituximab

Although many patients achieve virological response using INFα and ribavirin, several considerations still exist: only 50% patients carrying genotype 1, which is the most common genotype in Europe and Americas, respond. Also, pegylated form of INFα as well as ribavirin are contraindicated in patients with compromised renal function, which may prove puzzling when treating patients with severe renal involvement.

Rituximab is an anti-CD20 chimeric monoclonal antibody, which results in prompt depletion of circulating and tissue B cells. Cryoglobulins are produced by B cells. Hence, B-cell depleting biological therapy using Rituximab, holds theoretical promise of down-regulating the production and circulating levels of cryoglobulins. Following few cohort studies with promising results [12-16], a prospective randomized controlled trial to examine the role of rituximab in the treatment of patients non-responding to antiviral therapy has only recently been presented [17]. Twenty-four non-responders were included and followed for 12 months. Twelve patients were managed according to conventional strategies (maintain or increase immunosuppression) and twelve received rituximab (as administered in vasculitis: 375mg/m2 every week for 4 weeks). Following 6 months, 10 patients (83%) receiving rituximab achieved remission compared to 1 patient (8%) in the control group. At this point it appears that rituximab could be used in patients who did not respond to conventional treatment. In addition there is no restriction regarding renal function. However, the risk of serious infection remains an important consideration. Of note, in patients with high concentrations of IgM-k cryoglobulins with rheumatoid factor activity, complex formation with rituximab can occur resulting in severe systemic reactions.

A significant proportion of patients treated with conventional therapy despite sustained virological response relapsed during long-term follow-up, posing a significant question regarding the role of HCV on the pathophysiology of the disease [18]. Off label experience with rituximab to date may provide relevant insight: in patients receiving rituximab, relapses did not parallel virus load but coincided with the recovery of peripheral B cells. It has been proposed that B cell proliferation and thus subsequent cryoglobulin production can become independent of HCV overtime [3].

2.2.3. Vasculitis treatment: Plasmapheresis and conventional immunosuppression

Severe, life-threatening disease. Plasmapheresis is reserved for patients with acute, serious, life-threatening disease such as progressive renal failure, severe neuropathy, intestinal ischemia, alveolar hemorrhage and digital necrosis [19]. Removing cryoglobulins from the circulation presumably hinders immune-complex mediated vasculopathy leading to prompt improvement. However, following termination of plasma exchange a rebound overproduction of cryoglobulins may occur. Therefore, concomitant treatment aiming to mute cryoglobulin production is required. High dose glucocorticoids in conjunction with cyclophosphamide (CyP) represent the standard therapeutic regimen. Following the paradigm of ANCA-associated vasculitis, azathioprine and mycophenolate mofetil (MMF) are often used for remission maintenance or in the place of CyP when the disease is less severe (doses are presented in Table 2) [20]. Duration and efficacy of such treatment modalities

http://dx.doi.org/10.5772/54272

have not been assessed in controlled clinical trials. Consequently, therapeutic decisions are usually taken on an individual basis according to clinical response, personal history, comorbidity as well as the centre's experience to treat such patients.

Antiviral treatment is usually avoided until acute flare has been controlled [21, 22]. Exacerbation of the underlying vasculitis due to INFα and restrictions regarding ribavirin administration in patients with impaired renal function remain the main considerations. The same may apply to rituximab where monotherapy rather than combination with antiviral therapy is recommended by some authorities during the treatment of a severe disease [23]. Following remission of severe inflammatory phenomena, antiviral treatment should be administered.

Mild-to-moderate disease. Manifestations, such as purpura, arthralgias/arthritis, mild proteinuria/hematuria with normal serum creatinine or peripheral sensory neuropathy represent mild-to-moderate disease activity. In cases of HCV-related disease, viral clearance with combination therapy as described above is the initial treatment of choice.

Low-dose corticosteroids (<7.5–10 mg/day) can be administered for more efficient control of symptoms (arthritis/arthralgias, persisting purpura, etc.). Sequential or simultaneous administration [16, 24] of corticosteroids with IFNα did not influence the sustained virological response in treated patients. Nevertheless, whenever possible it is prudent to avoid corticosteroids during the initial course of antiviral therapy. Quick tapering of corticosteroids is also advised since long-term administration does not seem to grant a favorable effect on vasculitis, while can harm the liver function.

The use of immunosuppression in cyoglobulinaemic vasculitis is summarized in Table 3.

Drug	Dosage	Comments
Prednisolone	60 mg/day for 1 month tapered to 15 mg/day at 3 months	IV methylprednisolone 500-1,000 mg/day for 3 successive days in critical organ manifestations
Cyclophosphamide (CyP)	for 3-6 pulses	Oral CyP (2 mg/Kg/day) can be used
Rituximab IV	375 mg/m2/week for 4 pulses	In intolerance to CyP and in young patients with severe disease
Azathioprin	2 mg /kg/ day	
Mycophenolate Mofetil	2 g/day	In patients with moderate renal involvement who cannot take CyP
Plasmapheresis	three times weekly for two to three weeks	In critical organ manifestations

Table 3. Immunosuppressive treatment for cryoglobulinaemic vasculitis

2.3. Treatment of non-HCV mixed cryoglobulaenimic syndrome

According to current EULAR recommendations, patients presenting with mixed cryoglobulinaemic syndrome non-related to HCV or other disorder should be treated as patients with ANCA – associated vasculitis [8].

Although rare, cases associated to hepatitis B virus (HBV) have been documented. Antiviral therapy with lamivudine or entecavir has led to remission in isolated case reports. Myeloproliferative diseases and most commonly B cell lymphoma may also be the cause of mixed cryoglobulinaemia. Prompt diagnosis and appropriate treatments should be applied. Among autoimmune diseases, Sjogren's syndrome and systemic lupus erythematosus most commonly are associated with cryoglobulinaemia.

2.4. Special considerations

Patients with end Stage Renal Disease. Patients are treated with hemodialysis or peritoneal dialysis. Survival is comparable with with that of end stage renal diseases. Kidney transplantation can be performed. High rate of relapse has been recorded (up to 70%). However, recurrent disease does not lead to graft loss and thus relapse risk does not forbid transplantation in patients with end stage renal disease. Another concern in cases of HCV-related disease is that robust immunosuppression following transplantation may exacerbate HCV infection. Fortunately, this has proven to be the exception rather than the rule [25].

Cancer Risk. B-cell lymphoma has been reported in up to 25% of patients with mixed cryoglobulinaemic syndrome. Patients are usually diagnosed within 10 years. Low levels of gamma globulins may predate neoplastic transformation. Standard chemotherapy in combination with rituximab is usually required. HCV infection increases the B-cell lymphoma risk by 20-30% and is associated with increased frequency of liver cancer, which is diagnosed in up to 10% of patients [26].

2.5. Prognosis

Prognosis mainly depends on whether vital organ(s) are involved.

Most studies have examined glomerulonephritis (GN) where 10-year survival rate was reported to be 30-50%. However, therapeutic progress substantially improved prognosis since 10-year survival has recently been raised to almost 80%. Male gender, HCV infection, high cryocrit, low C3 and raised serum creatinine at baseline are considered bad prognostic factors. Intestinal ischaemia and alveolar haemorrhage have high mortality rates (>80%). In patients with HCV infection, carriers of genotype 2 and 3 along with early virological response have the best outcome. Of interest, changes of cryocrit level do not seem to correlate with clinical activity. It would be interesting, however, to examine whether the degree of solubility at 37°C or a decline in the temperature at which the cryoproteins precipitate might better correlate with response to treatment [27].

http://dx.doi.org/10.5772/54272

3. Henoch-Schonlein Purpura

Henoch-Schönlein purpura (HSP) is the most common vasculitis syndrome of childhood, although is also well described in adults. Clinical features include palpable non-thrombocytopenic purpura, particularly over the buttocks and lower extremities, arthritis (or arthralgia) affecting primarily large joints, diffuse abdominal pain and renal involvement with microscopic or gross haematuria, and/or proteinuria. There are also reports on the involvement of other organs, including lungs, brain and testes. Generally, it is a benign disorder that follows an intercurrent illness, usually an upper respiratory tract infection.

HSP is an immune complex-mediated small vessel vasculitis. Serologic studies document elevated levels of IgA and activation of the alternate pathway of the complement system. The characteristic histopathologic finding of HSP is leukocytoclastic vasculitis with IgA deposits with affected vessels.

Although prognosis is excellent in children with HSP, a small minority of patients develop long-term complications, and primarily renal disease. In adults, the risk of significant renal disease is increased. Management of HSP includes supportive care to ameliorate acute symptoms, as well as targeted treatment to decrease the risk of complications (usually due to gastrointestinal complications) and to prevent chronic renal insufficiency. Targeted treatment is summarized in Table 4.

3.1. Supportive management

Treatment of HSP is primarily supportive and includes adequate hydration and symptomatic relief of pain. Edema of the lower extremities and buttocks is improved with bed rest and/or elevating the affected area. Acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) help with mild rash and arthritis. However, NSAIDs should be used cautiously in elderly persons due to increased risk of renal impairment and gastrointestinal bleeding.

3.2. Targeted treatment

3.2.1. Glucocorticosteroids

Oral steroids. Oral steroids are used in patients with painful cutaneous edema, severe rash, scrotal and testicular involvement, renal involvement and abdominal pain [28]. There is some supportive evidence for the use of corticosteroids in severe abdominal pain. In a systemic review that included three randomized trials and 12 retrospective studies, prednisolone at a dose of 1 mg/Kg/day for two weeks or 2 mg/Kg/day for one week may decrease the intensity and duration of abdominal pain and may decrease the frequency of bowel intussusceptions and thus surgical interventions [29-31] .

Renal involvement is a common finding in HSP. Although the prognosis of HSP is excellent in children, persistent renal disease can cause long-term morbidity. This risk of significant renal disease is greater in adults with HSP [32]

However, it is not clear if corticosteroids decrease the likelihood of renal disease [29;30;32-39]. A meta-analysis suggested that early use of corticosteroids reduced the odds of developing persistent renal disease [29]. However, concerns are raised over the validity of this analysis, which included studies with different treatment protocols and follow-up time [36]. A more recent meta-analysis of four randomized controlled trials showed no significant difference in the risk of persistent renal disease at 6 and 12 months in children treated with prednisone for 2-4 weeks after initial presentation compared with placebo or supportive treatment [34]. Thus there are no convincing data to support the routine use of oral steroids as a measure to prevent renal disease in patients with uncomplicated HSP.

High dose steroids. Steroid treatment with high intravenous doses (pulses) and/or long term oral administration are the treatment of choice in acute HSP glomerulonephritis in children [32]. Methylprednisolone pulse therapy was evaluated in a prospective study with 38 children with severe HSP nephritis, defined as nephrotic syndrome at presentation and/or 50% or more crescentic glomeruli on biopsy [37]. Clinical recovery was achieved in 20 children. Renal biopsy in these children showed a significant decrease of the activity index with a decrease or disappearance of IgA deposits.

Steroids can be used alone or in combination with immunosuppressive agents (i.e., cyclosporin A, cyclophosphamide, mycophenolate mofetil, and azathioprine) [32].

3.2.2. Cyclophosphamide

Cyclophosphamide (CyP) is widely used in the treatment for the majority of vasculitides. In HSP, CyP has been used mainly for rapidly progressive glomerulonephritis (GN), while case reports of successful management of pulmonary hemorrhage also exist [33].

In a randomized controlled trial, 56 children with severe HSP nephritis were treated with oral cyclophosphamide (90mg/m^2/day) without steroids for 42 days. At final follow-up, 48.2% of children had full recovery, 39.3% had persistent abnormalities and 12.5% ended up with end-stage renal failure or death. No patient with crescents in 50% or more of glomeruli went on to full recovery. The authors concluded that CyP had no significant efficacy [39].

The combination of CyP with steroids has provided better outcome. In a retrospective study, high dose corticosteroids plus oral CyP (2mg/kg/day for 12 weeks) significantly reduced proteinuria in children with HSP GN [35]. Oral prednisolone (1.5 mg/kg/day) combined with an 8-week course of CyP (2 mg/kg/day) in 9 children with severe HSP nephritis, resulted in remission of proteinuria in 7 children [38]. Triple therapy with oral CyP (2.5mg/kg/day), methylprednizolone (30 mg/kg/day [maximum 1g/day], for 3 days), and intravenous urokinase (5000 U/kg/day [max 180.000], for 7 days) reduced protein excretion and mesangial IgA deposition compared with the group that received the same therapeutic combination without CyP [40]. In another study, combined therapy with intravenous pulse methylprednisolone (for 3 days), oral CyP (for 2 months), oral dipyridamole (for 6 months) and oral prednisolone (for 3 months) resulted in normalization of glomerular filtration rate in all but 1 patient [41]. Combined therapy with prednisolone, CyP, heparin/warfarin, and

dipyridamole, in 14 children with severe HSP nephritis, followed for 7.5 years, resulted in a significant improvement of histological grade of nephritis [42].

In adults, adding CyP to steroids provided no benefit in a 12-month, open-label trial of 54 patients with severe HSP GN [43].

3.2.3. Cyclosporin A

Cyclosporin A (CsA) is an effective immunosuppressive agent used for different immune-mediated glomerular diseases [32].

In a randomized study of of 24 children with nephrotic-range proteinuria or crescenting HSP nephritis, CsA was more efficacious compared to IV pulses of methylprednisolone [44]. In two retrospective studies by the same group, CsA plus steroids was found to be beneficial in HSP children with nephrotic syndrome [45,46]. In a retrospective study of 29 children with nephrotic-range proteinuria treated with CsA plus steroids, 23 achieved stable remission, while 6 patients became CsA-dependent [47]. In a clinical trial with a mean follow-up of 6 years all patients responded to CsA therapy (plus ACE inhibitors), however some patients developed CsA- dependent nephritis [48].

CsA plus steroids, either as initial treatment or after other immunosuppressive drugs in a small case series of 5 adult patients with HSP with nephrotic-range proteinuria showed beneficial effects on proteinuria and preservation of renal function, after a follow-up period of 5 years [49].

Overall, despite the data reporting proteinuria reduction by CsA in patients with HSP nephritis, this treatment is not supported by RCTs and cautiousness should be exercised for potential nephrotoxicity of CsA.

3.2.4. Azathioprine

Azathioprine is used in combination with steroids mostly in children with crescent HSP nephritis [32].

Azathioprine plus steroids showed beneficial effects in a clinical trial of 21 children with severe HSP GN. Treatment with either oral or intravenous (IV) corticosteroids led to comparable outcome [50]. Retrospective studies also support the use of combination of azathioprine with steroids for the treatment of severe HSP nephritis in children [51]. Early treatment with azathioprine plus steroids prevented progression of chronic kidney disease [52]. The combination was effective in improving histopathological changes [53]; however, 2 of the 10 patients treated with azathioprine showed definite tubulointerstitial nephritis at followup biopsy [54].

3.2.5. Mycophenolate mofetil

Mycophenolate mofetil (MMF) appears to be a promising therapeutic agent in many autoimmune diseases such as lupus nephritis, vasculitis and in IgA nephropathy.

There is limited evidence to support the use of MMF in HSP. Case reports [55-57] suggest a beneficial effect of MMF on HSP with complications. In six children in whom steroid therapy has failed, MMF was able to control complications and to sustain disease remission. MMF was well tolerated [58]. More recently, MMF along with ACE inhibitors reduced protein excretion and improved renal function in 12 children with HSP and nephrotic range proteinuria, who failed steroid treatment (20-25mg/kg/day) [59].

3.2.6. Rituximab

The efficacy of rituximab (RTX) in chronic HSP has been suggested by a case report. Three pediatric patients were treated with RTX for severe refractory chronic Henoch-Schönlein purpura, characterized mainly by neurologic and gastroenterological symptoms resistant to steroids and CyP. All 3 patients responded to 1 or 2 courses of RTX without serious adverse events [60]. In another case report one patient with moderate nephritis and severe skin HSP responded to RTX [61].

3.2.7. Plasma exchange

The addition of plasma exchange to common immunosuppressives and steroids have shown efficacy in patients with HSP and severe of extra-renal manifestations (alveolar and cerebral hemorrhage, haemorrhagic pancolitis, extensive vasculitic leg ulcers) [62-64]. Plasma exchange has also been used as sole treatment in patients with severe HSP nephritis with encouraging results [65,66].

3.2.8. Intravenous immunoglobulin

The clinical use of intravenous immunoglobulin (IVIg) has been extended beyond antibody-deficiency syndromes, to a wide variety of clinical conditions, such as neuroimmunological diseases, and systemic autoimmune diseases. Kawasaki disease was the first primary vasculitis in which IVIg had become the standard treatment of care. IVIg has also shown beneficial effects in patients with ANCA-associated vasculitis (AAV) refractory to standard therapy with prednisone and CyP [67]. In HSP, IVIg inhibited disease progression in isolated case reports [68,69].

3.3. Additional treatments

From a pathophysiological point of view, the removal of any source of chronic bacterial challenge, which may trigger HSP episodes, should theoretically be beneficial [70]. This is the reason why there are reports about tonsillectomy and periodontal therapy in children with HSP [71-73]. However, the therapeutic contribution of such approaches are difficult to evaluate since are commonly used in combination with other therapies.

Antithrombotic prophylaxis with warfarin, dipyridamole, and acetylsalicylic acid has been used along with immunosuppressive agents by several authors [70]. ACE inhibitors have been shown to be efficacious in reducing proteinuria and should be added at any level of proteinuria.

3.4. Emergencies

Patients with HSP may present with severe abdominal pain, gastrointestinal (GI) bleeding and renal insufficiency. Up to 50% of patients with HSP and GI manifestations have occult bleeding, but major hemorrhage occurs in only 5% and intussusceptions in 2% [74]. Other manifestations may include bowel infract, perforation and pancreatitis, which may require urgent surgical consultation.

Medication	Indication	Comments
Acetaminophen, NSAIDs	Arthritis, rash (mild)	Precautions: renal insufficiency and GI bleeding (for NSAIDs)
Oral steroids	painful cutaneous edema, severe rash, scrotal and testicular involvement, renal involvement and abdominal symptoms	Steroids may shorten the duration of abdominal pain and the risk of surgical interventions In few RCTs, short-course of oral prednisone does not prevent persistent renal disease
IV pulse steroids	Nephrotic range proteinuria, nephritic syndrome	
IV pulse steroids plus Immunosuppression	Rapidly progressive glomerulonephritis, pulmonary hemorrhage	CyP : no supporting RCT; serious side effects Azathioprine: no RCTs, cases of tubulointerstitial nephritis CsA: no RCTs, potential nephrotoxicity MMF: limited data Rituximab: limited data
Plasma exchange	Refractory HSP nephritis pulmonary and gastrointestinal hemorrhage, cerebral hemorrhage	
ACE inhibitors	Proteinuria	

Table 4. Medications used in the treatment of HSP

4. Idiopatic cutaneous vasculitis

Cutaneous vasculitis is a vasculitis confined to the dermis and is not a single disease. In fact, only less than 30% of cutaneous vasculitis can be defined as idiopathic. All other cases are systemic vasculitides, vasculitis associated with other rheumatic diseases (sys-

temic lupus erythematosus, rheumatoid arthritis), or vasculitis induced by malignancy, infection or medication/toxin. Therefore, one should search carefully for extracutaneous manifestations of vasculitis and obtain a detailed medical history. Also mimics of vasculitis, such as antiphospolipid syndrome, should be ruled out. Even idiopathic cutaneous vasculitis is not a single entity. An international consensus conference defined cutaneous leukocytoclastic angiitis as isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis [1]. This definition is controversial, since it requires biopsy for diagnosis and even biopsy is not diagnostic. Other terms used under the umbrella of idiopathic cutaneous vasculitis include hypersensitivity vasculitis, and urticarial vasculitis [75]. There are few points to consider in diagnosing cutaneous leukocytoclastic angiitis (CLA). First, CLA manifests with palpable purpura. On biopsy, cutaneous leukocytoclastic angiitis is characterized by leukocytoclastic vasculitis in upper to middle dermis (where small vessles are located), whereas necrotizing vasculitis in lower dermis and subcutaneous fat involves medium-sized vessels associated with cutaneous polyarteritis nodosa and other systemic vasculitides. Serum ANCA tests by immunofluorescence, with ELISA for MPO and PR3 to exclude ANCA-associated vasculitis, serum cryoglobulin test, to exclude cryoglobulinaemic vasculitis, and immunofluorescence for IgA deposits on skin biopsy, to exclude Henoch-Schonlein purpura, are necessary laboratory tests in diagnosing cutaneous leukocytoclastic angiitis.

Treatment of idiopathic cutaneous vasculitis depends on the severity of lesions and the extent of cutaneous involvement. For example, purpura is a manifestation of superficial dermal small vessel vasculitis with no serious consequences. Therefore any treatment should be with few if any side effects. However, it should be reminded that what initially appears to be isolated cutaneous vasculitis may be the presenting feature of an underlying disease, such as lymphoma or systemic vasculitis. Therefore, vigilance is required. Nodulal lesions and ulcers are caused by medium-sized vessels and suggest cutaneous polyarteritis nodosa or other systemic vasculitides Therefore, more intense treatment is required. It should be mentioned that there are no randomized controlled trials and treatment of idiopathic cutaneous vasculitis is based on case reports or small case series.

When cutaneous vasculitis is associated with a systemic disease one should treat the systemic disease. Also, any inciting agent, either drug or infective agent, should be removed. For instance, any infectious trigger should be treated with antibiotics. If food allergen is suspected, allergy testing is recommended, and if positive, elimination of the relevant food is tried, since low-antigen diet prevents recurrences of palpable purpura [76]. Drugs that are used with variable efficacy in idiopathic cutaneous vasculitis include non-steroidal anti-inflammatory drugs (NSAIDs), antihistamines (such as doxepin, loratadine, and cetirizine), colchicine, hydroxychloroquine (HCQ), dapsone, and prednisolone. However, no drug is universally efficacious. Colchicine inhibits neutrophil chemotaxis. Dapsone inhibits the alternative pathway of complement, and suppresses neutrophil chemotaxis. Hydroxychloroquine inhibits lysosomal enzyme release. The idiopathic leukocytoclastic cutaneous small vessel vasculitis is often self-limited and does not require specific treatment. Leg elevation, avoidance of excessive standing, and administration of

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NSAIDs or antihistamines usually relieve symptoms, such as pruritus and burning sensation. For persistent disease, colchicine is considered a drug of first choice [77]. Colchicine is effective in 50% of patients with cutaneous leukocytoclastic vasculitis within 2 weeks, although in a randomized controlled trial colchicine (0.5 mg twice daily) for a month was no more efficacious than topical emollients [78]. Patients with chronic cutaneous venulitis are usually resistant to treatment. Dapsone (100-200 mg daily) may be very effective in leukocytoclastic vasculitis and urticarial vasculitis. Dapsone appears to have synergistic effects with colchicine or pentoxifylline [79]. HCQ is more often used in urticarial vasculitis associated with connective tissue diseases. Prednisolone, at the initial dose of 0.5-1 mg/Kg/day for 2 weeks with rapid tapering, can be very effective in acute severe episodes. However, Idiopathic Cutaneous Small Vessel Vasculitis can be active for 10 years and prednisolone monotherapy is not recommended for chronic use. In difficult to treat cases, azathioprine may be used with low-dose prednisolone. Other medications that have been used include CsA (2.5-5 mg/kg/day, in two doses).

4.1. Urticarial vasculitis

Urticarial vasculitis(UV) is characterized by persistent (greater than 24 hours) urticarial skin lesions and leukocytoclastic vasculitis on histology. It is associated with low serum complement (hypocomplementaemic urticarial vasculitis, HUV) or normal serum complement levels (normocomplementaemic urticarial vasculitis, NUV). HUV is usually a systemic disease and associated with systemic lupus erythematosus (SLE) with autoantibodies against C1q. NUV is usually confined to the skin and rarely associated with SLE. Nearly 50% of patients with idiopathic UV have autoantibodies against IgE or IgE receptor.

Treatment of UV is based on manifestations. For mild skin lesions antihistamines, colchicines, dapsone, HCQ and prednisolone are used. The addition of reserpine (0.3-0.4 mg/day) to antihistamines may improve UV symptoms [80]. For extracutaneous disease or chronic necrotizing skin lesions prednisolone is used, often in association with azathioprine, mycophenolate mofetil (MMF), CsA, or CyP. IVIg and plasmapheresis have been used in difficult to treat urticarial vasculitis [76]. Rituximab, a monoclonal antibody against CD20, present on mature B cells, was successfully tried in a patient with UV with angioedema unresponsive to prednisolone, CsA and plasmapheresis [8].

4.2. Cutaneous polyarteritis nodosa

In mild cases, colchicine or NSAIDs may suffice. In moderate to severe cases, prednisolone is administered at an initial dose of 1 mg/kg/day, usually in conjunction with HCQ, dapsone, methotrexate, azathioprine, CyP, or intravenous immunoglobulin [81]. Mizoribine, an inhibitor of inosine monophosphate and guanosine monophosphate synthetase, which inhibits T and B cell proliferation, is also efficacious. Warfarin or clopidogrel are helpful adjuvant treatment [82].

5. Precautions

Certain precautions should be observed to reduce side effects of drugs used. CyP dose should be adjusted for renal function and age.

Patients should be checked for tuberculosis with chest x-rays and PPD skin test, and patients with latent tuberculosis should receive prophylaxis with isoniazid plus vitamin B6. Patients on IV pulse CyP, receive antiemetic drug (ondaserton) immediately prior to and 8 hours after the CyP pulse. On the day of IV CyP pulse, patients receive oral or IV hydration with 2-3 liters of fluid. They also receive IV 2-mercaptoethanesulfonate (mesna) (20% of CyP dose) immediately before and at 2, 4 and 8 hours after the CyP pulse to reduce irritation of urinary bladder. The dose of next IV CyP pulse is adjusted to keep nadir white blood cell (WBC) count (12-14 days after the IV pulse) >3,000/μL. The rate of leucopenia, infections, and gonadal toxicity is reduced in the IV pulse CyP compared to oral CyP regimen [83,84]. Oral mesna is also beneficial for patients on oral CyP.

According to a recent study ever-tobacco smoking and previous episode of hemorrhagic cystitis were strong predictors for the development of cancer in the urinary tract. Thus patients with these characteristics need close surveillance with urine cytology tests.

All patients receiving CyP are advised to take prophylaxis against Pneumocystis jiroveci with trimethoprime/sulphamethoxazole (800/160 mg thrice weekly).

Gonadal failure is a common side effect in patients treated with CyP, where the risk increases in parallel with the increase of the cumulative dose received. No standard care to preserve gonadal function has been proposed for patients with small vessel vasculitis under CyP. For similar issues encountered in female patients with systemic lupus erythematosus (SLE) two protocols exist: administration of leuprolide acetate with or without transdermal estrogen and depo-progesterone for contraception. Leuprolide should be administered 10-14 days prior to each CyP infusion. In men with SLE, administration of intramuscular monthly injections of testosterone has been proposed. Analogous approaches should probably be adopted for young patients with small vessel vasculitis at risk.

Patients on immunosuppression should not be vaccinated with live attenuated vaccines. They can and should be vaccinated with dead pathogens. Patients with granulomatosis with polyangiitis(Wegener's granulomatosis) exhibit adequate antibody [85] and cell-mediated immune response to influenza vaccines [86].

INFα may cause hepatic dysfunction and extreme caution is advised in patients with cirrhosis. PEG-INFα and ribavirin are contraindicated in renal impairment (creatinine clearance [ClCr] <50ml). Ribavirin can cause haemolytic anaemia.

Colchicine can induce gastrointestinal upset (diarrhoea, vomiting) and rarely cytopenia. Dapsone can cause granulopenia and severe haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Therefore, before initiation of dapsone, G6PD should be measured, and then full blood count regularly. Side effects of HCQ are rare and include retinopathy and cytopenias.

http://dx.doi.org/10.5772/54272

6. Conclusion

Small vessel vasculitis may be a manifestation of systemic vasculitis or may be confined to the skin. Therefore, biopsy of skin lesion with immunofluorescence and careful search for systemic disease are mandatory for the correct diagnosis. The treatment of cryoglobulinaemic vasculitis is based on the underlining aetiology. In HCV positive patients with severe vasculitic manifestations, immunosuppressives with plasmapheresis is the modality of choice. Anti-HCV treatment is administered after the control of inflammatory manifestations. In HCV-associated cryoglobulinaemic vasculitis with mild disease, anti-HCV treatment may suffice. HSP is usually a self limited disease. In patients with HSP complications, corticosteroids remain the main treatment. In severe refractory cases, plasmapheresis in conjunction with immunosuppressives have been tried. Idiopathic cutaneous leukocytoclastic vasculitis is most of the time a mild disease and does not require toxic medications. Rituximab is a promising new treatment for systemic or refractory small vessel vasculitis.

Author details

Christina G. Katsiari[1], Theodora Simopoulou[1] and Lazaros I. Sakkas[1,2*]

*Address all correspondence to: lsakkas@med.uth.gr

1 Rheumatology Clinic, School of Medicine, Faculty of Health Sciences, University of Thessaly, Larissa, Greece

2 Center of Molecular Medicine,Old Dominion University, Norfolk, VA, USA

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