DEFINITION AND CLASSIFICATION

Vasculites belongs to a heterogeneous group of diseases in which some or all Blood Vessels (BV) are the target tissue of an abnormal immune response. Clinically, it is a pathological process which is, in its’ acute phase, characterized by inflammation and BV wall necrosis that can, in its’ chronic stage, due to thickening of the wall, result in ischemia and neovascularization.

First mentioned by J. Hunter in 1790, only to be revisited 100 years later by Perls who provided the first histological image of retinal periphlebitis in Tuberculosis (TB) [1]. Retinal Vasculitis (RV) that was not infectious in nature (i.e. was idiopathic) was initially described by H. Eales in the year 1880, and thus the disease carries his name [2].

Vasculitis can involve only arteries; only veins (more frequently); arteries and veins; or capillaries (capillaritis).
Pathoanatomically and clinically, inflammation of the BV can be seen as sheathing and/muffling, whilst inflammation and necrosis of BV lead to focal and diffuse leakage from it, thus resulting in Macular Edema (ME).

RV can occur in conjunction with inflammation of various BV in the body (systemically) and/isolated (inflammation only affects retinal BV, in which case it is deemed to be an autoimmune response (autoimmune anti – retinal anti – S antigen vasculitis)). Laboratory tests for anti S antibodies in the blood depict that retinal anti S antibodies are more commonly associated with RV than they are with other uveoretinal inflammations [3]. Isolated RV can occur as part of infective Chorioretinitis (CR).

**Systemic vasculitis**

Systemic vasculitis (primary and secondary) is defined as an inflammation of BV localized in the eye, as well as in various other systems and organs, whose diagnosis requires that an overall, detailed examination (especially of the organs that are mostly affected such as the Central Nervous System (CNS); kidneys; skin; lungs; buccal and nasal mucus), be performed. Laboratory tests include various immune markers for each of the localizations.

RV as part of systemic vasculitis has both ocular and clinical manifestations.

RV can occur with/without any subjective symptoms, but however, if they do exist, they can be: decreased Visual Acuity (VA); floaters; and scotomas. In case of vasculitis, decreased VA may be either due to vitreal haze or to Macular Edema (ME). In some cases, all of a sudden, due to hemorrhages from the affected and/newly formed BV, there can be substantial decrease of vision.

**Clinical signs of RV**

Basic changes are in form of cuffing and sheathing of BV. More detailed description of ocular and systemic clinical signs can be found next to each one of the described diseases. However, it is important to point out that ophthalmological changes can be indicative of the nature i.e. etiology of systemic disease. Type and size of Retinal BV (RBV), involvement of both arteries and/ veins and/capillaries associated with other manifestations on the eye fundus (papilitis; intermediate uveitis; and others); vitreal changes; inflammation of the anterior segment; or in other words the entire clinical picture of ocular manifestations, can significantly aid in establishing the exact etiology of systemic disease.

RV can manifest in association with: anterior uveitis (in ±1/3 of patients [4]; scleritis (polyarteritis nodosa or Periarteritis Nodosa (PAN); Adamantiades - Behcet's disease (ABM); Systemic Lupus Erythematosus (SLE); and other collagen diseases); protein and cell vitreal Tindall (in nearly all cases of vasculitis, more commonly in severe cases); snow balls and snow banks in the underlying vitreous (intermediate uveitis and vasculitis as part of sarcoidosis); and dics atrophy (as consequence of retrobulbar neuritis in Multiple Sclerosis (MS).
Primary systemic vasculitides or systemic vasculitis

Primary systemic vasculitides or systemic vasculitis are defined based on presence of immune deposits in situ and size of vessels involved, and as such are grouped as inflammation of: 1) large BV (Horton’s disease (GCA); Takayasus’s arteritis); 2) medium BV (PAN; Kawasaki disease); 3) small BV (Wegener’s Granulomatosis (WG); Churg-Strauss Syndrome (CSS); Henoch-Schönlein Purpura (HSP)).

Secondary vasculitis

Secondary vasculitis is triggered by exogenous or endogenous factors which are able to bring about an autoimmune reaction to it. Secondary vasculitis can be divided into 4 groups: 1. vasculitis as part of an infectious disease (toxoplasmic chorioretinitis (ocular toxoplasmosis); Varicella Zoster Virus (VZV) and Herpes Simplex Virus (HSV) chorioretinitis; Human Immunodeficiency Virus (HIV) and Cytomegalovirus (CMV) retinitis); 2. neoplastic vasculitis (Masquerade syndrome); 3. Drug - induced vasculitis; 4. autoimmune diseases (SLE; Rheumatoid Arthritis (RA); polychondritis; Sjogren’s syndrome; Crohn’s disease; ulcerative colitis; Cogan syndrome; ABD; MS; sarcoidosis (sarcoid - systemic granulomatosis)) [5].

More detailed description of systemic and ocular manifestations and treatment (as per protocol) of some, most common, autoimmune noninfectious diseases, associated with primary or secondary vasculitis can be found further on in the text.

PRIMARY SYSTEMIC VASCULITIS

Primary Systemic Vasculitis of Large Blood Vessels

Giant cell arteritis – Horton's disease

Horton’s disease is a granulomatous necrotizing arthritis, described as temporal arteritis or Giant Cell Arteritis (GCA) with a predilection for large and medium sized arteries, especially for temporal superficial artery; ophthalmic artery; posterior ciliary arteries; and vertebral arteries.

Ocular manifestations

Ocular manifestations are anterior ischemic opticopathy; retinal and choroidal ischemia; uveitis; scleritis; and extraocular muscle disease. Most common cause for unilateral decrease of VA associated with GCA is optical neuropathy, and is to be differentiated from anterior, noninflammatory, ischemic opticopathy which, in the older population, occurs as consequence of atherosclerosis. Posterior ischemic opticopathy; central retinal artery occlusion; and diseases of other blood vessels (BV), are rare. GCA is easier to diagnose if there exist both systemic and ocular manifestations of the disease. Fluorescein Angiography (FA); color doppler test of the temporal artery; increased erythrocyte sedimentation rate (>50 in the first hour) and C reactive proteins, are diagnostic parameters for GCA. Certain diagnosis of GCA is achieved based on histological
findings of biopsied temporal superficial artery (infiltration of blood vessel wall with epithelial and giant cells).

Treatment of GCA requires that corticosteroids be ordained, and that treatment be initiated with pulse doses of methylprednisolone.

**Takayasu’s arteritis**

Takayasu’s Arteritis (TAK) is rare, segmented, aortal and main arterial branch necrotizing arteritis. Clinical signs that occur as consequence of occlusive vasculitis are: claudication of the extremities; and loss of peripheral pulse, while in the later stage of the disease there exists: facial skin atrophy; loss of hair and teeth; and lip ulcerations (as consequence of decreased blood flow in the anterior part of the face). Ischaemic heart disease and pulmonary hypertension occur due to narrowed vessels. Diseases of the carotid, such as ischemic syndromes and hypertension, manifest in the eye in the later stages of the disease. Decreased retinal and choroidal perfusion can result in ischemic optic neuropathy; choroidal ischemia; retinal and disc neovascularization; and secondary glaucoma. Treatment of TAK consists of corticosteroids and immunosuppressive drugs; retinal Laser Photocoagulation (LFC), and/ surgical intervention, performed in order to achieve reperfusion of regions that have been excluded due to Retinal Vein Occlusion (RVO).

**Primary Systemic Vasculitis of Medium Sized Blood Vessels**

**Polyarteritis nodosa or periarteritis nodosa**

PAN is a type of necrotizing vasculitis of small and medium sized BV. Clinical signs of the disease are peripheral neuropathy and kidney; gastrointestinal tract and myocardial diseases. PAN most commonly presents on the skin (as petechial polymorphic lesions) and subcutaneous nodules (places of necrotic infiltrates around small BV).

**Ocular manifestations of PAN**

Ocular manifestations of PAN are corneal marginal infiltrations and ulcerations; scleritis and episcleritis; anterior uveitis; orbital and diseases of the buliomotors, are a result of small BV occlusive inflammatory process. Small and medium retinal and choroidal BV vasculitis results in multifocal segmental blood flow exclusion on the fundus eye. Fluorescein Angiography (FA) depicts that initially there exist areas of hypofluorescence of ischemic areas that become areas of hyperfluorescence, which is indicative of the fact that occlusion of small BV occurs at the level of choriocapillaris. Seeing that small BV are affected more often than large and/ medium BV, PAN is in differential diagnosis with Acute Posterior Multifocal Placoid Pigment Epitheliopathy (AMPPE).

**Treatment of PAN**

High doses of corticosteroids; immunosuppressive agents; and plasmapheresis.
Kawasaki disease

Kawasaki disease is classified as vasculitis of small and medium sized BV, which commonly manifests in form of heart and BV diseases, and which is more common to the young population.

Ocular manifestations occur as consequence of complications, and are presented in the form of RV (more commonly periphlebitis); anterior uveitis; conjunctivitis and keratitis.

Treatment includes anticoagulants; immunoglobulin (intravenous); and plasmapheresis (in case of severe forms of the disease).

**PRIMARY SYSTEMIC VASCULITIS OF SMALL BLOOD VESSELS**

**Wegener’s granulomatosis**

Wegener’s Granulomatosis (WG) or Granulomatosis with Polyangitis (GPA), is multisystemic, granulomatous, necrotizing vasculitis. Granulomatous infiltrates are located either in the vessel wall or extravascularly, whilst the most common systemic manifestations are in the upper respiratory tract and in the sinuses; lungs; kidneys; CNS; and various other organs.

Ocular manifestations occur in 30 - 60% of cases and are characterized by granulomatous, necrotizing, infiltrates of lacrimal gland; orbit; sclera; and cornea. WG can be isolated in the orbit, thus manifesting as an orbital syndrome and/ be in differential diagnosis with pseudotumors of various other etiologies such as Tolosa Hunt [6]. Clinical manifestations of WG on the orbit can be: diplopia; posterior ischemic opticopathy; macular and disc edema, while clinical manifestations on the posterior segment of the eye can be in form of uveitis; occlusive vasculitis; and choriocapillaritis.

WG is additionally confirmed by the presence of cytoplasmic antineutrophil cytoplasmic antibodies (c - ANCA), a highly useful test for monitoring of both treatment and disease progression. Long-term treatment of WG consists of corticosteroids (in severe cases, pulse doses are administered) and/ immunosuppressive agents, but in very severe cases it is necessary to implement biological therapy.

**Churg-Strauss syndrome**

CSS is allergic angiitis, systemic disease that attacks small BV. It is similar to WG and PAN. Essential characteristic of CSS is formation of eosinophilic granulomas on BV of skin; kidneys; gastrointestinal tract; lungs; and the eye - where they can be localized on tarsal conjunctiva; peripheral cornea; and sclera. RBV diseases can lead to central Branch Retinal Arterial Occlusion (BRAO); retinal infarction; and anterior ischemic opticopathy. Increased erythrocyte sedimentation rate (ESR or sed rate); eosinophilia; and positive perinuclear antineutrophil cytoplasmic antibodies (p - ANCA) or c - ANCA in the blood are indicative of this disease.

Treatment of CSS consists of corticosteroids and immunosuppressive agents.
Henoch-Schönlein purpura

HSP, anaphylactoid purpura, is an autoimmune disease that mostly affects children but can, in some cases, also affect the older population. HSP is a form of vasculitis that affects small arterial vessels where inflammation causes BV of the skin; intestine; kidneys; and joints to start leaking. Clinical symptoms of HSP are: rash; joint pain and swelling; abdominal pain; and/or related kidney disease, including blood in urine (hematuria); melena; vomiting; and/or diarrhea. Systemic manifestations occur due to increased production of immunoglobulin A (IgA) and their accumulation in the BV wall.

Ocular manifestations of HSP include: episcleritis; uveitis; and vasculitides that correlate with those of the skin and joint. Treatment of HSP is comprised of corticosteroids and immunosuppressive agents.

SECONDARY SYSTEMIC VASCULITIS

Adamantiades - Behcet’s Disease

ABD; Behcet’s disease or syndrome; Silk Road disease or Morbus Behcet, is a multisystemic disease that can be localized on the eye; mucous; skin; CNS; and the joints. Systemic manifestations of ABD are: recurrent oral; genital; and intestinal ulcerations; skin lesions similar to those in erythema nodosum; big joints arthritis; epididymitis; thrombophlebitis; and diseases of the CNS. ABD is genetically determined disease (HLA B51+) that occurs as a result of increased reactivity to viral and bacterial antigens.

Ocular manifestations occur in 70% of cases and they include: anterior recovery serofibrinous uveitis with hypopyon; retinal vasculitis and total uveitis [4]. Occlusive vasculitis localized on arteries and/ veins is an essential ophthalmological manifestation of this disease. Narrowing and obliteration of RBV can lead to ischemia; disc atrophy; and ME [Figures 1a and 1b].
Increased blood coagulation (clotting) and tendency for thrombosis (thrombophilia) can either be consequence of primary antiphospholipid syndrome (factor V Leiden thrombophilia; methylenetetrahydrofolate reductase (MTHFR); prothrombin factor II, a vitamin K-dependent precursor of thrombin)); or secondary antiphospholipid syndrome (antiphospholipid antibodies (APLA)) [7]. Most severe forms of RV and uveitis which are associated with ABD can lead to blindness and thus require that immunosuppressive and/ immunomodulatory treatment be applied on time.

**Systemic lupus Erythematosus**

SLE is a multisystemic disease in which the immune system reacts to its’ own antigens localized in the nucleoplasm; nucleus; cytoplasm; and cell membrane. Formed antigen - antibody complex activates complements and leads to a third type of reaction (immune complex reaction). Systemic manifestations of SLE are on the skin; mucous; musculoskeletal system; kidneys; CNS; heart; and on the lungs.

Ocular manifestations are on the conjunctiva (conjunctivitis sicca); cornea (marginal corneal infiltrates); and sclera (diffuse and nodular scleritis). Second most common manifestation of SLE is lupus retinopathy, which is initially characterized by cotton wool spots (isolated or surrounded by hemorrhages) [Figure 2]. Progressive lupus retinopathy can lead to occlusive arteritis; capillary dropout and retinal ischemia of the same; neovascularization; and intravitreal and retinal hemorrhages.
Individuals with systemic lupus, in its’ active phase, have raised levels of antiphospholipid antibodies; Antinuclear Antibodies (ANA); and cryoglobulines, and decreased values of complement components 3 (C3) and 4 (C4).

Treatment of SLE includes: corticosteroids; immunosuppressive agents; Nonsteroidal Anti-Inflammatory Drugs (NSAID); anti-malaria medication; biological agents; and plasmapheresis.

Due to their association with systemic vasculitis, the following systemic diseases will be further looked at: sarcoidosis (systemic noncaseating granulomatosis) and MS (demyelinating disease of the CNS and RV).

**Sarcoidosis**

Sarcoidosis, or sarcoid, is a multisystem inflammatory disease of unknown etiology that manifests as systemic noncaseating granulomas (growth of tiny collections of inflammatory cells).

Most common manifestation of sarcoid is pulmonary hilar lymphadenopathy and chronic fibrosis; only to be followed by cutaneous (skin) sarcoid which presents with erythema nodosum; nodular and papillary (small nipple like) projections on the skin; and erythematous lesions on the face. Lymphoglandular sarcoidosis can affect lacrimal and salivary glands as well as all other lymph glands throughout the body. Skeletal sarcoidosis is highly uncommon, can have musculoskeletal manifestations, and is predominantly localized on bones; and hand and wrist joints. Neurosarcoidosis is a condition featuring granulomas in various tissues, involving the CNS (in base of the brain and in the spinal cord) thus resulting in neurological dropouts which are associated with cerebral compression by the granuloma. Reliable diagnostic tests that are used to confirm and monitor active sarcoidosis are (increased): Angiotensin-Converting Enzyme
(ACE); calcium levels in blood and 24h urine; biopsy (if sarcoid granulomas are obtainable), and hyposensitivity; Kveim-Siltzbach; skin tests which depict lowered skin sensitivity to specific antigens. Bronchoscopy and Nuclear Magnetic Resonance (NMR) spectroscopy are used as part of diagnostic procedure of pulmonary and neurosarcoidosis respectively.

Ocular manifestations of sarcoidosis occur in 25-50% of individuals, and although anterior uveitis is the most common manifestation, changes on the posterior segment of the eye still occur in 10-45% of individuals, and may have very serious complications [4,8]. Manifestations of ocular sarcoidosis on the fundus eye are: (single or multiple) sarcoid granulomas; intermediate uveitis; retinal periphlebitis (more common than periarteritis); and ME (as complication). In the acute phase of the disease there can be hemorrhages and ME formation, while in the chronic phase of the disease, in places of chorioretinal granulomas, there are atrophic areas (patches) that can pose as a differential diagnostic problem in multifocal choroidopathy (idiopathic multifocal inflammatory condition / chorioretinopathy that belongs to a group of White Dot Syndromes (WDS)). In 20% of cases there is neovascularization; vitreal hemorrhage; and retinal detachment [5]. Seeing that corticosteroids are recommended therapy for individuals with more pronounced symptoms of sarcoidosis, immunosuppressive and/ immunomodulatory agents are included as part of the treatment plan only in cases where corticosteroids alone do not achieve the desired effects.

**Multiple Sclerosis**

MS is a demyelinating disease of the CNS. Demyelization is a process whereby neuronal myelin sheath is damaged, i.e. there is damage of the protective covering (myelin sheath) that surrounds nerve fibers in the brain and the spinal cord. Macrophage-like cells of the brain and spinal cord (microglia) as well as macrophages engulf and absorb myelin (mixture of proteins and phospholipids forming a whitish insulating sheath) following which astrocytes (star-shaped CNS glial cells) form plaques (confirmed via an NMR) from the connective tissue. So, as myelin acts as an insulator, thus increasing the speed of transmission of all nerve signals, demyelization disrupts neuronal conduction pathways in the white matter. Seeing that phagocytes are of key importance for MS it is highly likely that viruses and bacteria damage the myelin sheath thus resulting in an autoimmune response to it, and Cerebrospinal Fluid (CSF) thus may contain myelin antibodies (oligoclonal immune response).

Frequent ocular, and possibly one of the primary manifestations of MS is optic retrobulbar neuritis. During the course of his studies, Rucker was first to deduce that in 20% of cases there exists association between coating of retinal veins and MS [4]. On the other hand, incidence of retinal periphlebitis varies from 8.5-33%, and the most frequent type of uveitis is intermediate which, if it occurs in association with active retinal periphlebitis and various neurological manifestations, is indicative of MS [4]. It is deemed that ±25% of individuals with RV and intermediate uveitis, especially if they are HLA B7+ or DR15+, will develop MS [4] [Figures 3a and 3b].
Treatment of MS includes corticosteroids (pulsed doses); Azathioprine (AZA); interferon β1a/β1b; immunoglobulin (intravenous); and muscle relaxants.

Complications of Retinal Vasculitis

RV can be associated with both anterior and posterior ocular complications. Complications which occur on the anterior segment of the eye are: cataract and secondary glaucoma (neovascular and corticosteroid induced), and complications which occur on the posterior segment of the eye, and which can lead to substantial visual loss, are: ME; disk atrophy; peripheral retinal complications (breaks; retinoschisis; retinal ischemia; neovascularization; and retinal detachment).

Macular Edema

Macular Edema (ME) is defined as liquid accumulation in external plexiform and internal nuclear layer, as well as swelling of Muller cells. It occurs as consequence of increased leakage from retinal perifoveal capillaries and consequential macular thickening that, if it lasts for longer than 6 months, is seen as chronic in nature.

Prolonged macular traction caused by Epiretinal Membranes (ERM) can also be one of the possible causes of both ME and various other retinal complications that can substantially affect visual outcome [9,10].

Prevalence and incidence of ME depend on chronicity of the inflammation and persistence of traction ERM on the macula. Permeability and size of the edema do not have to correlate with VA, however chronic ME and/ persistent ERM traction can lead to disintegration of the photoreceptor layer and thus decreased VA [9,11].
**Why does macular edema occur?**

According to the mechanism of occurrence, ME can be ischemic (associated with ischemic maculopathy) and nonischemic (focal and diffuse).

Ischemic ME can occur due to relative macular ischemia, as consequence of capillary nonperfusion on the macular border which results in increased avascular region (>500µm), and cell damage which occurs once it is >1000µm. On the other hand, vascular occlusion results in protein leakage from BV and so the edema is formed.

**Focal or Cystoid Macular Edema (CME)** occurs when perifoveal liquid accumulation in the external plexiform layer (Henle's fiber layer). Cysts which occur are of radial orientation and look like a sunflower.

**Diffuse ME** is diffuse liquid accumulation in the macula that leads to swelling and thickening of the macula.

Besides ischemic and nonischemic ME retinal wrinkling and contraction of ERM can cause tractional macular edema. Generally, ME is caused by distortion and traction of ERM on intraretinal BV which results in disturbance of retinal microcirculation and decreased capillary flow, and in the meantime, loss of apposition between retina and Retinal Pigment Epithelium (RPE). In order to provide a dry, normal, medium i.e. that vitreal hyaloid membrane remains attached to the retina, there must be an equilibrium between the vitreous body; retina; and the choroidea, or in other words there must be a constant flow of liquid from the subretinal space to the choroidea, in which inner and outer Blood-Retinal Barriers (BRB) play an essential role. So, the role of BRB is to separate blood from the surrounding retinal tissue; regulate flow of blood and proteins from the surrounding tissue and, in case of inflammation, efflux of leukocytes from blood into the surrounding tissue.

**Passive forces** (Intraocular Pressure (IOP)) push fluid into the retina, while osmotic pressure and active forces provide active transport of matter on the level of RPE, thus drawing liquid and substances from the retina into the choroidea. Under physiological conditions, these forces are strong enough to maintain this subretinal space dry. Therefore, disruption, i.e. breakdown of BRB, has an essential role in ME formation, and depending on the state of BRB, ME can be intra and extra cellular.

**Intracellular edema** occurs in case that BRB is intact but retinal cells swell (due to changed ionic arrangement between intra and extracellular spaces (sodium concentration in the cells is higher, cytotoxic edema)).

**Extracellular edema** is directly connected with both inner and outer BRB breakdown (state of which is most precisely confirmed by FA).

**Inner BRB** (on the capillary level) consists of occludens and adherens gap junctions, while outer BRB consists of junctions between cells RPE (tight adherent and desmosomal). Disruption
of the inner and outer BRB leads to fluid accumulation in the retina, and under pathological conditions, while disruption of outer BRB leads to fluid accumulation in the subretinal space. Vascular leakage and breakdown of inner BRB in RV, can be due to numerous mediators such as: leukocyte adhesion molecules and Nitrogen Monoxide (NO) prostaglandins; leukotrienes and cytokines (interleukin - 6 (IL - 6); interleukin 10 (IL - 10)), while partial retraction of the edema can be under the influenced of both tumor necrosis factor α (TNF α) blockers and Anti Vascular Endothelial Growth Factor (anti VEGF), which are thus used as part of the treatment plan [12-15].

Diagnostic methods and tests for assessment of macular function are: VA test (Snellen chart); contrast sensitivity and color vision test; Electro Retino Gram (ERG); and Amsler grid eye test. Necessary, reliable methods used in diagnosis of transparent media are: fundoscopy; FA; and Optical Coherence Tomography (OCT) [16]. With the aid of FA, which is deemed to be diagnostic golden standard, one can register fluorescein leakage from capillaries and RBV and thus judge the state of inner BRB; accurately determine localization / areas of capillary leakage, as well as the type of edema. This method provides clear difference between diffuse ME (poorly defined regions of hyperfluorescence and abnormal capillary leakage) and CME (cystic spaces localized in the external plexiform layer are filled with fluorescein and look like a flower), and if any ME lasts for an extended period of time, cystic spaces can join, and result in irreversible macular disorder [17]. If RPE layer is damaged (disordered) as consequence of inflammatory process in the choroid, outer BRB can be viewed with the aid of Indocyanine Green Angiography (ICG) (choroidal BV contain free ICG molecules) [18]. While FA is considered to be the golden standard for analysis of inner BRB, OCT is a noninvasive, high resolution (3-5µm) imaging technique used to obtain in vivo cross sectional images of the retina and measure macular thickness (volume; average and central macular thickness) and changes on the level of the photoreceptor layer i.e. state of photoreceptors; pigment epithelium; subretinal space; Internal and External Limiting Membranes (ILM and ELM) [19]. It is a very useful tool used to determine the difference between diffuse and cystoid ME; measure the size of retinal cysts and amount of subretinal fluid; as well as to analyze changes of the vitreoretinal interface and the state of subretinal neovascular membrane (from abortive to developmental stage). Thus, as it can be repeated, OCT is especially useful qualitative and quantitative technique for followup of both treatment and evolution of macular changes; size and localization of vitreoretinal adhesions; size of ERM and its’ distance from the retinal surface [Figures 4 and 5].
Figure 4: Multiple sclerosis; OCT; treatment followup.

Figure 5: Sarcoidosis; OCT; treatment followup.
THERAPEUTIC APPROACH

Evolutive RV associated with systemic vasculitis is treated with appropriate therapy, which depending on the underlying disease, is in compliance with existing therapeutic protocols. RV in systemic vasculitides is treated with corticosteroids; immunomodulatory and immunosuppressive agents; as well as with biological therapy.

Corticosteroids

Corticosteroids are considered to be the golden standard for treatment of noninfectious inflammatory diseases.

Mechanism of action of corticosteroids: after entering the cell steroid molecules bind to the cytoplasmic steroid receptors, steroid - receptor protein complex then passes through the nuclear membrane and binds to sites known as Glucocorticoid Response Elements (GRE) which directly control transcription of various mRNA and translation of protein end products (immunomodulatory effect). Corticosteroids act by: 1) inhibiting enzyme phospholipase A2 which participates in breakdown of cell membranes phospholipids and in this manner decrease leukotriene and prostaglandine production (which dilate the BV thus leading to efflux of cells from them and their accumulation in the tissue i.e. inflammatory reaction); 2) decreasing BV permeability thus decreasing production of interleukin-1 (IL-1), whilst on the other hand increasing fluid reabsorption along the RPE; 3) decreasing production of Vascular Endothelial Growth Factor (VEGF) (achieved through inhibited production of platelet deriving and activating factor) thus strengthening the BRB; 4) inhibiting angiogenesis induced by VEGF and IL-6 by blocking their receptors and thus binding to them [20-22].

Corticosteroids are applied both systemically and/ locally [23].

Systemically applied corticosteroids can be very effective in treatment of bilateral RV which begins at high doses (1mg/kg/day) that are then decreased to a maintenance dose (5mg/day). In case of severe form of RV associated with systemic vasculitis such as WG; MS; GCA; and others, pulse doses of methylprednisolone are to be applied (250-1000mg, 3-5 days). Following pulse doses, corticosteroids are to be applied in doses of 1mg/kg/day. Once tapering is initiated it is not to be greater than 10% of the previous dose, and at 10-15 day intervals.

RV associated with systemic vasculitis is chronic and bilateral in nature and thus requires long-term treatment which consists of corticosteroids; immunomodulatory and/ immunosuppressive treatment (steroid spearing agents). Besides systemic agents treatment of ME requires parabulbar/intravitreal application of corticosteroids. Long-term treatment with corticosteroids can have many systemic side effects such as: arterial hypertension; Diabetes Mellitus (DM); duodenal ulcers; suppression of adrenal gland; etc.

Corticosteroids are applied locally in form of drops; subconjunctival injection (dexamone); parabulbar injections; methylprednisolone (40mg every 3-4 weeks); and intravitreally (slow
release agents). Locally applied drops penetrate the cornea and achieve high concentration in the anterior chamber (±2h after application), but it should be noted that oil drops provide longer lasting effects as opposed to soluble ones. On the other hand, corticosteroids applied topically for treatment of posterior uveitis and ME which occurred as consequence of uveitis and RV is disputable, and there are controversial, opposing views regarding this matter. Namely that locally applied, in form of drops, they penetrate the sclera and cornea and can positively affect ME [24].

Corticosteroids inhibit interaction between leukocytes, while their accumulation and adhesion to the endothelium, mediated by Nitrogen Monoxide (NO) and adhesion molecules, prevents them from exiting through the endothelial BV wall. Leukocyte adhesion to the endothelium and their accumulation are responsible for both damage caused to the endothelium and for their efflux into the surrounding tissue. Corticosteroids also lead to decreased production of VEGF and reduced production of arachidonic acid end products (i.e. prostaglandins), therefore allowing Muller’s cells to, via endogenous adenosine, release accumulated fluids and thus increase task channels. This process results in reduced release of potassium and adjusted down regulation of kir 1 protein [25]. Periocular application (subconjunctival injection) of dexasone can be effective in treatment of unilateral inflammations as, applied in such manner, it is quickly absorbed and directly affects site of inflammation; resolves anterior uveal inflammation and consequently affects ME [26].

It is deemed that parabulbar application of slow release corticosteroids (especially in case of unilateral ME not associated with active RV) is more effective in treatment of ME as opposed to subconjunctival and local application of dexasone and corticosteroid drops respectively. Parabulbar application of corticosteroids can be performed in two ways i.e. subtenonially or with the aid of Noziks’ technique (posterior injection), and in both cases corticosteroids are slowly absorbed through the sclera and it is in close contact with the posterior pole and the macula [27]. In case of ME, parabulbar application can be repeated 4-6 times within a period of 3-4 weeks, but one must bear in mind that this, and numerous other types of corticosteroid delivery systems, may be accompanied by various complications such as accidental penetration; increased IOP; endophthalmitis; and/ cataract formation.

Corticosteroids that can be applied intravitreally in a form of a depot injection of Triamcinolone Acetonide (TA) (Kenalog, 4mg of which can be repeated every 3-5 weeks) or slow release agents such as: Ozurdex (intravitreal slow release corticosteroid implant of 0.7mg dexamethasone i.e. 25 times stronger than cortisol and safer than TA, which has no toxic effects on the RPE and retinal cells and doesn’t cause pseudo-endophthalmitis, full effect of which last for 3months and partial effects for another 3months but as it begins to wear off the eye may slowly become inflamed again); and Retisert (a slow release intravitreal implant which over a period of ±30months releases 0.59mg fluocinolone acetonide locally to the posterior segment of the eye at a nominal initial rate of 0.6μg/day that decreases over the first month to a steady state of 0.3-0.4μg/day) [28-31]. Intravitreal application of corticosteroids is the most effective application of the drug, which can be accompanied by complications such as endophthalmitis (rarely); elevated IOP; and
rapid cataract formation, and both parabulbar and intravitreal applications are associated with limited drug duration effects that require repeated use, and carry increased risk of infection and precarious placement.

In the long term, locally applied corticosteroids can lead to numerous complications such as: secondary glaucoma; cataract formation; recovery herpetic keratitis.

**Immunomodulatory and Immunosuppressive Therapy**

Drugs commonly used for treatment of RV in the systemic vasculitides and have immunomodulatory and immunosuppressive effects (transcription inhibitors, anti-metabolites, anti-mitotic agents) are: cyclosporin A (CSA); Methotrexate (MTX); Mycophenolate Mofetil (MMF); azathioprine; and Cyclophosphamide (CYC) [32,33].

**Cyclosporin A (3-5mg/kg/day)**

CSA consists of 11 amino acid peptides produced by fungus Beauvaria nivea. CSA acts on lymphocyte proliferation by blocking T cell receptors for genes encoding numerous lymphokines and enzymes necessary for activation of resting T cells. CSA also inhibits calcium-dependent intracellular signal transcription of nuclear factor of activated T cells (NF-AT) which is responsible for production of a strong T cell mitogen IL-2.

It is deemed that 20-50% of CSA is absorbed in the gastrointestinal tract; that the highest serum levels are achieved within 3-4 hours; that 90% of it binds to protein; and that, even though only a relatively small amount of CSA penetrate it, there are some indications that it is still able to reach ±40% of its’ serum concentration in the eye.

Due to hypertension, nephrotoxic and hepatotoxic effects of the drug, it is necessary to regularly monitor side effects of CSA and to, once a month, test concentration of CSA in the blood (normally it is supposed to be ±100 pg) thus appropriately adjusting its’ dose.

Absolute indications for the use of CSA in ophthalmology are: ABD; sympathetic ophthalmia; Vogt-Koyanagi-Harada syndrome (VKH); as well as severe forms of bilateral uveitis, while it is to be used in case of uveitis of other etiology and RV only if they are very severe and resistant to other drugs [34]. Most clinicians believe that higher concentration of CSA in the eye is achieved when it is administered in conjunction with corticosteroids, explanation of which probably lies in the fact that greater permeability of the barrier is achieved as a result of corticosteroids thus allowing more CSA to penetrate into the eye.

Reducing CSA may result in relapse which would at the same time, in order to control the inflammation, require that CSA be replaced with other agents such as MMF.

**Methotrexate (5-25mg/week)**

Even though MTX was initially used in treatment of childhood leukemia today its’ use has widened to include not only lymphoblastic leukemia and CNS lymphomas but also inflammatory
diseases of varying etiology such as rheumatic diseases, systemic vasculitides (ABD; SLE; PAN) [35]. MTX is a folic acid antagonist which inhibits synthesis and renewal of DNA and transcription of RNA as, by competitively and irreversibly binding to the enzyme dihydrofolate reductase, it disrupts transition of dihydrofolate into tetrahydrofolate, which is the main factor in synthesis of purine and thymine. Inhibitory effects of MTX are specific for each cell cycle which exerts its’ activity in its’ S phase. Inhibition of dihydrofolate reductase can clinically be achieved by leucovorin, a fully functional coenzyme of folic acid.

**Mycophenolate Mofetil (CellCept, 30mg/kg/day)**

Seeing that MMF is a strong, selective, non-concurrent, irreversible, inhibitor of Inosine-5’-Monophosphate Dehydrogenase (IMPDH) it inhibits de novo pathway of guanine synthesis without incorporating into the DNA. T and B lymphocyte proliferation depends on purine synthesis, whilst other cell types can use various other salvage pathways, and thus it is deemed that MMF has powerful cytostatic effects on the lipmhocytes. It inhibits proliferative response of T and B lymphocytes on both mitogenic and allospecific stimulation. MMF is used in treatment of both systemic and RV [36].

**Azathioprine:** (Imuran, 1-2.5mg/kg/day, 50-100mg in a single or divided dose).

AZA is an antimetabolite which inhibits purine; adenine; and guanine synthesis thus blocking DNA and RNA replication and cell division (especially that of B lymphocytes). Following oral application, AZA is quickly absorbed and metabolized from glutathione S transferase into 6-mercaptopurine, which is then, via an enzyme, metabolized into its’ inactive components. It is used in treatment of both various ocular autoimmune diseases and systemic vasculitis (ABD, VKH, sympathetic ophthlalmia I idiopathic pars planitis) [37].

**Cyclophosphamide:** (Cytophosphane, Cytoxan and Neosar, 2 – 3mg/kg/day)

CYC or INN is a synthetic antineoplastic drug (prodrug) chemically related to nitrogen mustards. It is deemed that hepatic cytochrome P450 oxidase converts CYC into active metabolites of phosphor amide mustard and 4-hydroxycyclophosphamide which target 7 nitrogen atom of guanine to form guanine-thymine cross-links in the DNA thus leading to miscoding, DNA breaks, and phosphodiester bond formation following DNA break repair. CYC is biotransformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. CYC is usually used in combination with other medicines, and was primarily used in treatment of lymphoma while its’ use has since widened to include various forms of systemic vasculitides (ABD, WG, polyarteritis) but due to its toxicity it is only used in case that other medication is not effective enough [38].

**Biological Therapy**

Besides immnosuppressive agents, treatment of inflammatory immune disorders requires that biological treatment directed towards various cytokines in the inflammatory cascade be applied.
Recent studies have shown that besides lymphocyte and macrophage products, cytokines which are key molecules for ocular inflammatory cascade are: TNF $\alpha$, interferon $\gamma$, IL-1; IL-2; and IL-10. New anticytokine agents i.e. biological agents aimed towards cytokines and their receptors, are applied in cases where previously applied treatment was not efficient enough.

**Interferon $\alpha$:** (Interferon $\alpha$2a, 6miliona IU/day)

Over the past couple of years, if ABD and Inflammatory Bowel Disease (IBD) are resistant to immunosuppressive therapy, interferon $\alpha$ has been used instead.

**Daclizumab:** (Zenapax, 1mg/kg/ 2-4 weeks, intravenous)

Daclizumab is monoclonal antibody directly aimed against CD25 subunits of human IL-2 receptor on active T cells thus blocking their IL-2 mediated activation. Besides being sufficiently efficient in transplant surgery this agent is, in combination with AZA; CSA or corticosteroid therapy, used as part of uveitis treatment plan (VKH; Bird shot retinopathy; and WDS) [39].

**Infliksimab:** (Remicade, 3-10mg/kg, 1-2/month)

Infliksimab is a monoclonal antibody which interferes with TNF thus joining to well known receptors TNF 1 (which binds to soluble TNF) and TNF 2 (which binds to membrane TNF). Infliksimab can be used in treatment of RA; Crohn’s disease; psoriasis; ankylosing spondylitis; HLA associated uveitis and severe forms of vasculitis (especially ABD) [40].

**Etanercept:** (Enbrel, 25mg/ 2 – 3 weeks)

Etanercept is recombinant TNF receptor (P75)-Fc (fusion protein which inhibits TNF $\alpha$) and which binds to extracellular TNF $\alpha$, thus preventing binding of native receptors and inhibiting signal downregulation. Etanercept has been successfully ordained in case of: RA; Juvenile Idiopathic Arthritis (JIA); ankylosing spondylitis; psoriatic arthritis; and mucocutaneous manifestations of ABD [41].

**Rituximab:** (Rituxim, 375mg/m2/week, 4-8 weeks intravenously)

Rituximab is genetically engineered monoclonal antibody directed towards CD20 glycoproteins located on the surface of ‘normal’ B lymphocytes. Besides its’ role in treatment of B cell lymphoma, by targeting B cells, this agent is used as modulator of antibody mediated inflammatory response. Rituximab has successfully been used as part of the treatment plan of ABD [42].

**Anti VEGF treatment**

VEGF is connected with numerous mechanisms which cause ME. VEGF disrupts inner BRB through NO, which is important for aggregation and adhesion of leukocytes for endothelial cell wall, and disruption of the same; as well as for increased permeability of capillary endothelial cells (edema formation) [43]. On the other hand VEGF disrupts external BRB whereby, through activation of Protein Kinase C (PKC), it stimulates occludin phosphorylation (phosphorylation of
tight occluding junctions) thus, due to intercellular junction permeability, leading to disruption of outer BRB and edema formation.

Anti VEGF therapy includes: receptor fusion proteins; anti VEGF aptamers; and monoclonal antibodies.

**Ranibizumab**: (Lucentis, 10mg/ml/month)

Ranibizumab is humanized monoclonal antibody fragment (Fab) that binds to all isoforms of VEGF-A, thus preventing binding of VEGF-A to receptors VEGFR-1 I VEGFR-2 [44].

Ranibizumab is applied intravitreally once a month, and if a single intravitreal application of Ranibizumab is not enough, then, after the first 4 months, it may be applied as a single injection every 3 months thereafter. Intravitreally applied Ranibizumab decreases macular and retinal edema as well as Choroidal Neovascularization (CNV).

**Pegaptanib**: (Macugen, 0.3mg/90μL intravitreally applied every 6 weeks)

Pegaptanib is anti VEGF aptamer, synthetic oligonucleotide, which has high affinity and sensitivity for VEGF isoform 165 (VEGF165) [45].

**Bevacizumab**: (Avastin, 1.25 - 2.5mg, intravitreally)

Bevacizumab is an angiogenesis inhibitor, which slows formation of new BV. It is a recombinant humanized monoclonal antibody, which through inhibition of vascular endothelial growth factor A (VEGF-A) blocks angiogenesis [46]. Many ocular diseases may lead to blindness due to the fact that they damage the retina and, as RBV grow abnormally and leak fluid, lead to separation of retinal layers. Seeing that this abnormal growth is caused by VEGF, application of bevacizumab successfully inhibits VEGF thus not only slowing this growth but also decreasing permeability and ME in both uveitis and DM [47,48]. In treatment of proliferative (neovascular) eye diseases, and particularly for CNV in AMD, ophthalmologists are using intravitreally applied bevacizumab [49].

**Treatment of Macular Edema**

In case that systemic therapy is not part of the treatment plan, ME as complication of vasculitis is to be treated with local medication and/ surgically.

While deciding on the appropriate treatment of ME in case of RV it is important to make note of the following: is ME unilateral or bilateral; is ME acute or chronic; is ME ischemic or nonischemic; and of what etiology is the ME?

Even though the consensus has not been made as to how and when to treat ME, there are varying opinions. Namely, that: 1. ME is to only be treated if it is associated with an inflammation; and 2. ME is to be treated if it is chronic, even though there is no active inflammation on the eye fundus.

Besides previously mentioned corticosteroids, the following agents are used in treatment of ME: NSAID and carbonic acid anhydrase inhibitors.
Nonsteroidal Anti-Inflammatory Drugs

Mechanism by which NSAID work is based on inhibition of enzyme cyclooxygenase and thus on inhibited degradation of arachidonic acid end products [50]. Some NSAIDs act on other mediators i.e. when high doses of diklofenac retard inhibit leukotriene formation which, during the course of inflammation, increases cellular infiltration [51]. On the other hand, as flow of chlorides, and consequentially passage of fluids through the RPE, is driven by NSAIDs they are also deemed to be good modulators. So, NSAIDs are used both in the treatment of, and in prevention of, CME.

Topical NSAIDs which are primarily used in prevention and treatment of ME following cataract surgery, and which have over the past couple of years been used as part of additional therapy in prevention of ME associated with ocular inflammation and retinal vasculitis are: ketorolac tromethamine 0.5%; indomethacin 1%; and diclofenac 1% [52-54].

Carbonic Acid Anhydrase Inhibitors: (stimulators of RPE pumps)

Under normal circumstances, 70% of the fluid is removed from the retina into the choroidea via metabolic transport, so that inhibition of enzyme which is important for fluid transport leads to resolution of ME. RPE functions can temporarily or permanently be decreased due to inflammation, and repeated inflammation can lead to vascular incompetence of the pump, while stimulation of the same with this medication can, in ±1/3 of cases, result in resolution of the edema [55].

Carbonic acid anhydrase inhibitors change polarity of RPEs ionic transport system by inhibiting carbonic acid anhydrase and γ glutamine transferase which leads to increased transport through the RPE (from subretinal space into the choroidea) thus decreasing ME. Additionally, carbonic acid anhydrase directly impacts the retina and RPE by raising acidification of subretinal space. Carbonic acid anhydrase inhibitors such as acetazolamide and topical dorzolamide and brinzolamide better affect ME which is not chronic in nature.

Besides the previously mentioned agents, biological agents such as anti- IL-6 and anti-TNF (cytokines of which have been proven to correlate with uveitic ME) are used as part of the ME treatment plan [13, 56-59].

Laser Photocoagulation and Macular Edema

Besides medication, treatment of ME requires that, in order to stabilize the BRB, retinal LFC be applied. Energy from the laser coagulates necrotic RPE cells thus leading to proliferation of adjacent RPE cells and stabilization of tight junction BRB bonds [60].

Grid LFC is applied in case of uveitic ME as it destroys cells surrounding the affected region, and in doing so decreases their need for oxygen which thus diffuses from the choroidea into the retina where it increases arteriolar pressure and decreases hydrostatic pressure in capillaries and venules [61,62]. So, greater flow of oxygen in the arterioles, reduced hydrostatic pressure in capillaries and venules, lead to decreased edema i.e. reduced permeability.
Surgical Intervention

Tractional ME is caused by ERM contraction that leads to retinal layering; decreased pressure within retinal tissue; and at the same time, increased hydrostatic pressure difference between BV and retinal tissue which leads to ME. Complete release of Vitreomacular Traction (VMT), or in other words release of ERM, provides resolution of macular cystic spaces and ME, as well as better VA.

On the other hand, vitrectomy is seen as a method with the aid of which it is possible to remove the vitreous; increase oxygen transport between the anterior and posterior segments of the eye; and remove numerous vitreal inflammatory mediators responsible for edema formation ((IL-6); VEGF and platelet derived growth factor).

References
5. Stanojevic- Paovic A. Uveitis; Med University of Belgrade 2008; 105-144.


