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STEROIDS AND RADIOTHERAPY FOR THYROID-ASSOCIATED ORBITOPATHY

High-dose glucocorticoids (GC), preferably via the intravenous route, are the first-line treatment for severe and active thyroid-associated orbitopathy (TAO). High-dose intravenous pulse therapy with glucocorticoids (IVGC) is more effective and better tolerated than oral GC. Several randomized controlled trials found a response rate of 70-80% in patients treated with IVGC compared with approximately 50% in patients treated with an equivalent course of oral prednisone. The risk-benefit ratio is favorable overall and IVGC is preferentially administered for the treatment of active and severe TAO. IVGC act via suppression of the immune system in two different ways: a genomic and a non-genomic pathway. While the non-genomic pathway appears to be responsible for the quick effects only a few minutes after application, the genomic pathway determines the long-time effects. IVCG effectively modulate the effector cells (B and T cells) and the orbital target cells, i.e. orbital fibroblasts and pre-adipocytes. IVIG inhibit the release of pro-inflammatory mediators i.e. cytokines and prostaglandins and significantly reduce the titer of the disease relevant thyroid-stimulating immunoglobulins. Thus, discussion regarding IVGC for TAO has shifted from whether this therapy should be used, to how best to select patients most likely to benefit without major side effects and which treatment protocol optimizes efficacy and minimizes morbidity. This assumes accurate assessment of disease severity and activity and suggests that the therapy should be administered only in centers having expertise in the evaluation and treatment of patients with TAO. When IVGC are not logistically possible, oral GC remains a reasonable, although less effective, alternative to IVGC that might be considered. Orbital radiotherapy has been shown to potentiate the effects of oral GC, but there is no evidence that it has the same synergistic effect when steroids are administered intravenously. With respect to orbital radiotherapy, several randomized trials and meta-analyses have proven the beneficial effect of orbital irradiation regarding a clinically relevant amelioration of motility disturbances of the eye muscles. Indeed, the combination of GC and radiotherapy in the early stage of active TAO with impaired motility has proven to be superior to either monotherapy. In line with this, the recently drafted 2015 ETA / EUGOGO guidelines strongly recommend that patients with moderate-to-severe active TAO and present diplopia or

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disturbances of eye muscle motility be treated with a combination of oral GC and orbital irradiation. Both oral and IV GC may be associated with severe adverse events, which are more frequently reported in daily IVGC application. Investigational studies prior to therapy include assessment of liver function and hepatocellular integrity with consideration of hepatic ultrasound to investigate morphology. In addition measurement of viral markers for hepatitis and fasting serum glucose levels are recommended. Contraindications to therapy include evidence of recent viral hepatitis, significant hepatic dysfunction, severe cardiovascular morbidity, severe hypertension, and inadequately managed diabetes. Liver enzymes, glucose levels, and blood pressure are best monitored monthly during treatment.