Corticosteroids and Immunosuppressives

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Corticosteroids overview

- Indications
- Periocular
  - Orbital floor
  - Sub-Tenon
- Intraocular
  - Intravitreal injection
  - Intravitreal device
- Oral
- Intravenous
- Prescribing and side-effects

Corticosteroids

- Produced by the adrenal cortex
- Classified into three categories based on their primary physiological roles
  - Glucocorticoids
  - Mineralocorticoids
  - Sex hormones
- Basic structure of all steroids is similar and there is a degree of functional overlap

Equivalent anti-inflammatory doses of corticosteroids

- Prednisolone 5 mg equivalent to:
  - Betamethasone 750 µg
  - Cortisone acetate 25 mg
  - Deflazacort 6 mg
  - Dexamethasone 750 µg
  - Hydrocortisone 20 mg
  - Methylprednisolone 4 mg
  - Prednisone 5 mg
  - Triamcinolone 4 mg

Glucocorticoid therapy

- High glucocorticoid activity is of no advantage unless it occurs with relatively low mineralocorticoid activity
- Prednisolone has predominantly glucocorticoid activity and most commonly used for for long-term disease suppression
- The suppressive action of a corticosteroid on cortisol secretion is least when given as a single dose in the morning

Indications

- Oral/Intravenous
  - Failure of periocular, intraocular steroid
  - Bilateral non-infectious posterior segment disease
  - Prophylaxis prior to cataract surgery
Intravenous methylprednisolone

- Few studies
- Usually used as rescue therapy and an alternative to high dose oral therapy
- Dosage varies but often 1g for 3 days
- Given as slow infusion 45-60 minutes in 100 mls normal saline
- Potential side effects

Initiation of oral steroid therapy

- High dose oral e.g. prednisolone 60mg (non-enteric coated) daily for 2 weeks then taper (or 1mg/kg/day)
- (H₂ blocker/PPI, osteoporosis prevention)

Don’t forget!

- Varicella status
- CXR
- BP
- Urinalysis
- Baseline DXA scan
- Steroid card
- COUNSEL THE PATIENT

Administration of oral steroid

- Alternate day therapy
  - Requires a normal or moderately responsive pituitary/adrenal axis
  - Prednisolone causes hypothalamic-pituitary suppression for 12-36 hours
  - Allows the hypothalamic/pituitary axis to regain responsiveness on the day the patient is not receiving the drug
  - May require patient education

Termination of systemic therapy

- Rate and degree of withdrawal depends on
  - Activity of underlying process
  - Rate of recovery of the endogenous hypothalamic/pituitary/adrenal axis
  - A completely suppressed hypothalamic/pituitary/adrenal axis may take 9-12 months to recover if the patient was on daily therapy for > 6 months

Termination of systemic therapy

- No tapering is usually necessary if the patient has been on systemic therapy for < 7-10 days
- Patients on long-term steroid can have daily dosages tapered to 10mg prednisolone fairly rapidly as this level is still above physiological endogenous production
- Below 10mg the dosage must be tapered much more slowly
Side-effects of steroids

- Systemic
  - Too many to mention
  - Mineralocorticoid
  - Glucocorticoid
- Local
  - Raised IOP
  - Cataract

Corticosteroid-induced bone disease

- Glucocorticoid therapy is the most common cause of secondary osteoporosis and the leading iatrogenic cause of the disease
- Often, the presenting manifestation is fracture, which occurs in 30 to 50% of patients receiving long-term glucocorticoid therapy
- Glucocorticoid-induced osteoporosis predominantly affects regions of the skeleton that have abundant cancellous bone, such as the lumbar spine and proximal femur

Steroid side-effects

- The loss of bone mineral density is biphasic; it occurs rapidly (6 to 12% loss) within the first year and more slowly (approximately 3% loss yearly) thereafter
- However, the risk of fracture escalates by as much as 75% within the first 3 months after the initiation of therapy, typically before there is a substantial decline in bone mineral density, suggesting that there are adverse effects of glucocorticoids on bone that are not captured by bone densitometry

An increase in the risk of vertebral and hip fractures occurs rapidly after the start of treatment and has been reported to occur with doses as small as 2.5 - 7.5 mg of prednisolone per day
- In a cohort study involving patients 18 - 64 yrs, continuous treatment with 10 mg of prednisone per day for more than 90 days, as compared with no exposure to glucocorticoids, was associated with an increase in hip fractures by a factor of 7 and an increase in vertebral fractures by a factor of 17

1 in 3 women and 1 in 12 men > 50 yrs will suffer a fracture of the hip, wrist or spine as a result of osteoporosis
- Bone fractures can cause considerable pain and disability
- 50% of people who suffer a fractured hip lose the ability to live independently
- Around 20% of people who fracture a hip die within a year, as a result of their fracture
Bone densitometry

- Dual x-ray absorptiometry (DXA scan)
- Lower spine and one hip - two main areas at risk of osteoporotic #
- 1/10th dosage of a CXR and takes 10-20 mins
- Produces a printout of bone density compared to a reference range of young healthy adults
- Difference calculated and expressed in SD: T score
  - 0 and -1 SD (normal)
  - -1 and -2.5 SD (osteopenia)
  - below -2.5 SD (osteoporosis)

Corticosteroid-induced osteoporosis in patients with uveitis

- 129 uveitis patients
- On steroids for 13 weeks to 31 years (mean 3.6 years)
- Total dosage 1.29 - 166.6g (mean 16.85g)
- Mean daily dose 2.8 - 41mg (mean 13.6mg)
- 62 patients (48%) had additional risk factors for bone loss
- 17 patients (13.2%) used prophylaxis against bone loss

Corticosteroid-induced osteoporosis

- Bone densitometry:
  - Normal in 72 patients (55.8%)
  - Abnormally low in 57 patients (44.2%)
  - Osteopenia in 37 (28.7%)
  - Osteoporosis in 20 (15.5%)
- Symptomatic fractures in 7 patients
  - 3 had normal bone densitometry
  - 1 had osteopenia
  - 3 had osteoporosis
- Following bone densitometry further action taken in 51 patients

Steroid-induced cataract

- Posterior subcapsular
- Can be observed 1 year after equivalent dosage of 15mg/day prednisolone
- Occurs in about 25% of patients with RA
- 20mg/day for e.g. 4 years virtually all patients will develop cataract
- Patients with RA have a higher incidence
- Renal transplant patients also more susceptible

Steroid-induced raised IOP

- NOT a steroid “responder”
- Ocular or systemic administration of glucocorticoids can elevate IOP, depends on:
  - Individual responsiveness
  - Dose and potency of the glucocorticoid
  - Ocular bioavailability and metabolism
  - Route of administration
  - Duration of treatment
  - Genetic disposition

Counselling of side-effects

- We investigated patient knowledge and understanding of oral corticosteroid side effects, and tried to ascertain the amount of information provided by doctors prescribing these drugs
- Prospective questionnaire survey of 33 patients on oral corticosteroid
- Questionnaire survey of 30 Ophthalmologists of different grades
Do oral steroids always work?

- 30% of patients fail to achieve disease control at tolerable systemic doses and continue to have an increased immune response with poor clinical outcome
- Percentage of steroid resistant patients
- A subpopulation of steroid refractory (SR) peripheral blood CD4(+) T cells has recently been identified
- Potential target for intervention with anti-IL-2 therapies


Immunosuppressives - overview

- Definition
- Common immunosuppressives and mode of action
- Which drug, route and dose?
- Cost
- Evidence base
- Prescribing and monitoring
- Patient-centred care / Communication

- NOT a talk on every immunosuppressive in current practice

Immunosuppression - definition

- Suppression of the immune response to control autoimmune diseases
- Treatment that suppresses immune function where it is contributing to the disease process - includes immune-mediated diseases of the eye

Ocular inflammatory disorders have great potential for visual morbidity and visual loss

- Despite the vast expansion of therapies, and in particular biologics, there remains a dearth of level 1 evidence (from RCTs, systematic review of RCTs, and meta-analyses) for their efficacy in ocular inflammatory disease
- Moreover, we remain clinically constrained by potential toxicity of such immunosuppressants or immunomodulators, which may restrict long-term use or even prevent adequate enough immunosuppression
Indications

- Failure of local therapy
- Complications of local therapy
- Bilateral disease
- Active systemic disease
- Inability to reduce prednisolone to less than 10mg/day
- Unacceptable corticosteroid side-effects
- Certain uveitis entities – Behçet, VKH, sympathetic, birdshot

Key points

- In order to be effective treatment must be given
  - For a treatable lesion
  - At an adequate dose
  - Via the most appropriate route
  - For an appropriate length of time
  - Balance risks vs benefit
- Assessment of activity vs damage
- These drugs may be slow to act and need to have the dosage increased slowly

You MUST know

- Which drug most likely to be effective
- The dose and route
- How it works
- Side-effects
- How to monitor for side-effects
- What to do if side-effects
- Be able to communicate effectively with patients, doctors and other healthcare workers

Classes of drugs

- Antimetabolites
  - Methotrexate
  - Azathioprine
  - Mycophenolate mofetil
- T cell inhibitors
  - Ciclosporin
  - Tacrolimus
  - Sirolimus
  - Vinclozolin
- Alkylating agents
  - Cyclophosphamide
  - Chlorambucil
- Biologics
  - Anti-TNF agents
  - Rituximab
  - Interferons

Methotrexate

- Potent inhibitor of dihydrofolate reductase - limits the production of thymidylate which is essential for DNA synthesis and cell division
- 7.5-25 mg/week oral/sc
- Monitor blood count, hepatic and renal function
- Need to give Folic acid supplements (but not on day of methotrexate)
Azathioprine

- Purine nucleoside analogue
- Interferes with DNA replication and RNA transcription
- Mainly used as a steroid sparing agent
- Doses of approximately 2mg/kg
- Bone marrow suppression
- TPMT levels

TPMT

- Thiopurine S-methyltransferase (TPMT) is the primary enzyme responsible for thiopurine drug-based metabolism
- TPMT enzyme activity determines the amount of thiopurine-based drugs that are able to be metabolized
- In a Caucasian population approximately 89% have normal enzyme activity, 11% intermediate activity and 0.3% low or non-detectable levels
- Patients with low TPMT enzyme activity (poor metabolizers) are considered TPMT-deficient and at high risk for dosage-related side-effects
- TPMT-deficient patients accumulate higher concentrations of thiopurines when they receive standard dosages, greatly increasing the potential for drug-induced toxicity

Mycophenolate (mycophenolic acid)

- Originally used to prevent transplant rejection
- Selective inhibitor of purine synthesis
- Blocks T and B cell DNA synthesis
- Inhibits inosine monophosphate dehydrogenase, the enzyme which controls the rate of synthesis of guanine monophosphate in the de novo pathway of purine synthesis used in the proliferation of B and T lymphocytes
- Effective in EAU
- Effective in humans but relatively few studies
  - Uveitis
  - Scleritis
  - OMMP

Myfortic™ Vs Cellcept™

- Myfortic™
  - 720 mg bid (2 x 360 mg tablets)
  - Mycophenolate sodium - salt
  - Active moiety: mycophenolate
  - Delayed-release, enteric-coated
  - Released in small intestine

- Cellcept™
  - 1000 mg bid (2 x 500 mg tablets)
  - Mofetil ester - prodrug
  - Active moiety: mycophenolate
  - Immediate release
  - Released in stomach

Calcineurin inhibitors

- Potent immunosuppressants that reversibly inhibit T-cell proliferation and prevent release of pro-inflammatory cytokines by blocking the activity of the calcium-regulated serine-threonine phosphatase calcineurin, an enzyme found in cell cytoplasm
- Calcineurin inhibitors also block lymphokine production and release, fibroblast proliferation, and vascular endothelial growth factor expression

Ciclosporin

- An immunosuppressant of fungal origin (Beauveria nivea)
- Calcineurin inhibitor
- Binding to intracellular immunophilin receptors and blocking calcium-dependent intracellular transcriptional signalling of NFAT leading to inhibition of IL-2 production
- Dosage 2-5 mg/kg/day in divided doses
- Requires appropriate monitoring - renal function (creatinine), lipids, BP
Side effects

- Nephrotoxicity
- Hypertension (particularly in combination with corticosteroid)
- Excessive hair growth
- Gingival hyperplasia
- Tremor
- Parasthesiae
- Stopping the drug abruptly may lead to a significant relapse

Tacrolimus (Prograf)

- A macrolide - found in fungi although produced by a type of bacterium, Streptomyces tsukubaensis
- Similar action as ciclosporin
- Potentially nephrotoxic
- Recent trial showed that patients on combination therapy with corticosteroid could have their corticosteroid dose reduced and continue on tacrolimus monotherapy

Voclosporin

- Calcineurin inhibitor
- Double masked RCT for uveitis!!!
- The FDA and they have recommended that an additional clinical trial be conducted
- This is being conducted by Lux Biosciences

Rapamycin (sirolimus)

- A macrolide - a product of the bacterium Streptomyces hygroscopicus
- Not a calcineurin inhibitor
- Inhibits the response to IL-2 and thereby blocks activation of T- and B-cells
- Few clinical studies – SAVE study (subconjunctival and intravitreal)
- Now an intravitreal trial (Santen)

Prescribing and monitoring side-effects

- Who prescribes?
  - Ophthalmologist?
  - Rheumatologist?
  - GP?
- Who monitors?
  - Ophthalmologist?
  - Rheumatologist?
  - GP? Shared care guidelines must be in place
  - Immunosuppression Nurse?
Immunosuppression Nurse

- Counselling
- Point of contact
- Monitoring
- Liaising with GPs and other specialties
- Therapy - iv

Patient-Centred Care

- 'Providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions'
- Is multi-dimensional
  - Compassion, empathy and responsiveness to needs, values and expressed preferences
  - Co-ordination and integration
  - Information, communication and education
  - Physical comfort
  - Emotional support, relieving fear and anxiety
  - Involvement of family and friends

Compliance, Adherence, Persistence, Concordance

- Compliance
  - How a patient’s behaviour matches the prescriber’s advice
- Adherence
  - How the patient’s behaviour matches agreed recommendations from the prescriber
- Persistence
  - The length of time from commencement to discontinuation of a prescribed treatment (is often employed as an outcome for studies investigating adherence)
- Concordance
  - A complex idea relating to the patient/prescriber relationship and the degree to which the prescription represents a shared decision

Patient information

- Uveitis patient information groups
  - Uveitis Information Group: www.uveitis.net
  - Behçet’s Syndrome Society: www.behcoets.org.uk
  - Birdshot (chorioretinopathy) Uveitis Society: www.birdshot.org.uk
  - Deutsche Uveitis Arbeitsgemeinschaft e.V.: www.duag.org
  - Inflamoeil: asso.orpha.net/INFLAM
- Generic drug leaflets
  - Arthritis Research UK: www.arthritisresearchuk.org

Key points

- Therapies are potentially hazardous
- An understanding of the drugs - their mechanism of action and potential side effects is essential
- Careful monitoring must be carried out and in many cases treatment is best undertaken in conjunction with Physicians who have experience in using these drugs and understand the disease - need good communication
- No live vaccines
- Be aware of new treatment modalities
- Important that doctor and patient appreciate lack of good clinical trials
- Document the patient carefully
- Remember adequate precautions regarding birth control