Glucocorticoids in paediatric rheumatology

A. Ravelli[1,2], B. Lattanzi[1], A. Consolaro[1], A. Martini[1,2]

[1]Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini, Genova, Italy; [2]Università degli Studi di Genova, Genova, Italy.

Angelo Ravelli, MD
Bianca Lattanzi, MD
Alessandro Consolaro, MD
Alberto Martini, MD

Please address correspondence to:
Angelo Ravelli, MD,
Pediatria II,
Istituto G. Gaslini,
Largo G. Gaslini 5,
16147 Genova, Italy.
E-mail:
angeloravelli@ospedale-gaslini.ge.it

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ABSTRACT

Glucocorticoid (GC) drugs are the most potent anti-inflammatory agents available for the treatment of paediatric rheumatic diseases. These medications are used for the management of extra-articular features of systemic juvenile idiopathic arthritis and are the mainstay of therapy in children with juvenile systemic lupus erythematosus, juvenile dermatomyositis, and systemic vasculitis. The general objective of GC therapy is to limit the maximal dose and the exposure to the highest doses to what is needed to achieve disease control and, then, to gradually taper the dose until the minimum level sufficient to maintain disease quiescence over time is reached. High-dose intravenous "pulse" methylprednisolone administration is sometimes chosen to treat the most severe or acute manifestations of systemic inflammatory diseases. The rationale that underlies this treatment modality is to achieve an immediate, profound anti-inflammatory effect and to lessen toxicity associated with long-term continuous therapy in moderate to high daily doses. Intra-articular corticosteroid (IAC) injection is a safe and rapidly effective treatment for synovitis in children with JIA. Triamcinolone hexacetonide is the optimal corticosteroid preparation. Local injection therapy is used most frequently to treat oligoarthritis, but the strategy of performing multiple IAC injections to induce disease remission, while simultaneously initiating therapy with second-line or biologic agents, has been proposed also for children with polyarticular JIA. Administration of GCs is associated with potentially deleterious adverse effects, some of which can be irreversible. This highlights the need of a judicious use of these medications and a careful monitoring of their toxicity.

Introduction

The earliest reports on the use of glucocorticoid (GC) drugs in children with rheumatic diseases date back to the 1950s and 1960s (1). These medications are the most potent anti-inflammatory agents available for the treatment of these conditions, but are associated with substantial toxicity when administered systemically in high doses. Some side effects may result in non-reversible damage, such as growth failure, which is especially worrisome in young children. Therefore, when the use of these drugs is considered, the risk/benefit ratio must be carefully weighted.

The overall aim of GC therapy is to limit the maximal dose and the exposure to the highest doses to what is needed to achieve disease control and, then, to taper gradually the dose until the minimum level sufficient to maintain disease quiescence over time is reached. A child treated with these drugs should be under the care of a physician who is experienced in the management of the specific disease and in handling the risk of GC side effects.

Indications

In juvenile idiopathic arthritis (JIA), the use of systemic corticosteroids is mainly restricted to the management of the extra-articular manifestations of systemic-onset disease. These include high fever unresponsive to non-steroidal anti-inflammatory drugs (NSAIDs), severe anaemia, myocarditis or pericarditis, and macrophage activation syndrome (2-5). High-dose "pulse" intravenous methylprednisolone (10–30 mg/kg/day to a maximum of 1 g/day on 1 to 3 consecutive days) (see articles on p. S-81 and p. S-85) is effective in controlling these features, but the effect is often short-lived. Therefore, continued GC therapy with oral prednisone (1 to 2 mg/kg/day to a maximum of 60 mg/day in a single or divided daily doses) is frequently necessary.

A short course of low-dose prednisone (*e.g.* 0.5 mg/kg/day) may be considered for alleviating pain and stiffness in patients with severe polyarthritis refracto-

ry to other therapies or while awaiting the full therapeutic effect of a recently initiated second-line or biologic agent. Short-term systemic corticosteroid administration may also be indicated for chronic iridocyclitis unresponsive to topical therapy.

GCs are the mainstay of drug therapy in children with other systemic inflammatory conditions, such as juvenile systemic lupus erythematosus (JSLE), juvenile dermatomyositis (JDM), and systemic vasculitis (6).

In JSLE, constitutional symptoms, skin disease, serositis, or musculoskeletal symptoms are managed with oral prednisone 0.5–1 mg/kg as single dose or, occasionally, split doses. The presence of major organ involvement or life-threatening manifestations, namely proliferative glomerulonephritis, CNS disease, or severe haemolytic anemia or thrombocytopenia, warrants the administration of high-dose GCs, either as pulse intravenous methylprednisolone (as above) or oral prednisone 2 mg/kg/day (maximum 60-80 mg/day) in divided doses.

High-dose daily GCs (*e.g.* up to 2 mg/kg per day of prednisone, often in divided doses) constitute the standard treatment of JDM. Because children with this disease may absorb GCs poorly, perhaps as a result of gastrointestinal vasculopathy, early treatment with pulse intravenous methylprednisolone is preferred by some paediatric rheumatologists (7).

High-dose intravenous methylprednisolone therapy has been recently advocated as "rescue therapy" for children with Kawasaki disease who are unresponsive to repeated doses of intravenous immunoglobulin or relapse after such therapy (8). The potential benefit of GCs in the initial management of this disease is controversial, however.

In Henoch Schönlein purpura, GC therapy is advised to treat severe gastrointestinal disease or haemorrhage and to relieve pain of severe orchitis. The use of CSs to prevent renal disease in children with uncomplicated Henoch Schönlein purpura is not recommended (9).

GCs, administered either orally or as intravenous pulses, are the preferred initial treatment for other forms of systemic vasculitis, such as polyarteritis nodosa, Wegener granulomatosis, Takayasu arteritis, and microscopic polyangitis.

Adverse effects

Overall, the side effects of GCs in children are similar to those observed in adults. Because the general toxicity of GCs is described in other articles of this Supplement, only the adverse effects that are unique to childhood will be addressed.

Growth suppression is the most serious long-term consequence of GC therapy in paediatric patients. It occurs in children who are receiving prolonged therapy in doses greater than 0.2–0.3 mgkg/day of prednisone, increases with higher doses and is almost universally seen when divided doses are used (10). However, wide inter-individual variation exists in the severity of growth suppression and the minimal dose required to suppress growth. The mechanism of GC-induced growth suppression in children is unclear (11).

These medications have been shown to inhibit the production of somatomedin C (insulin-like growth factor I). In addition, their general inhibitory effect on cell growth and cell division probably contributes to growth failure. However, growth suppression, though worsened by GC therapy, may be a consequence of the underlying disease process. In JIA, particularly in the systemic-onset subtype, growth retardation can occur without GC therapy (12). Furthermore, there is evidence suggesting that growth retardation is much more severe in patients with JIA than in those with JSLE receiving equivalent doses. The effect of growth hormone in improving height in children with GC-induced inhibition of growth is controversial.

Another potential harmful effect of continued GC administration in young children is delayed puberty, which is due to the long-lasting suppression of the hypothalamic-pituitary axis and is often associated with growth failure (13, 14). Although pubertal delay is generally a temporary phenomenon, it may have irreversible consequences because it may contribute to hamper some important physiological milestones (that are also affected by GCs), such as growth spurt or bone mass accretion. These losses may not be regained once puberty develops and lead to final short stature and premature osteoporosis.

Minimising toxicity

The deleterious effects of GCs may be lessened by choosing a preparation with a relatively short half-life. Prednisone is the drug most often selected for oral therapy. Due to its enhanced glucocorticoid and minimal mineralcorticoid actions it has an optimal risk/benefit ratio. Although some reports have claimed that deflazacort, an oxazoline derivative of prednisone, may have a bone-sparing effect compared with prednisone, the evidence is unclear. Both the anti-inflammatory effect and the toxicity of GCs increase with larger doses and more frequent administration. Morning administration has less capacity to suppress the pituitary than do administration later in the day (which blunts the surge of ACTH that normally occurs during sleep).

Reduction in GC dose must be gradual and should be tailored to the child and the disease. At moderate to high doses (*e.g.* 40–60 mg/day), reductions of 5-10 mg are usually possible, whereas at lower doses (*e.g.* 5–10 mg/day) smaller reductions may be needed. Further dose tapering should be lead to switch, whenever possible, to an alternate-day regimen. A too rapid dose decrease may cause noxious withdrawal effects, such as steroid pseudorheumatism or pseudotumour cerebri. There is no experience in children with rheumatic diseases on the use of slow-release GC formulations (15).

There are no established guidelines for the prevention of GC-induced osteoporosis in paediatric patients. Several open studies have suggested that children with rheumatic diseases receiving GCs may benefit from calcium and vitamin D supplementation (1). The bisphosphonates have also been studied as a potential treatment for GC-induced osteoporosis (16, 17). However, many uncertainties persist regarding use of these drugs in paediatrics, including

which bisphosphonate is preferred, what should be the initial dose, and how long treatment should be continued. Furthermore, little is known about the duration of the antiresorptive effect once bisphosphonates are discontinued in younger patients.

Prolonged corticosteroid therapy may lead to suppression of hypothalamic-pituitary-adrenal function that can be slow in returning to normal. If not recognised, this complication places the child at risk for vascular collapse, adrenal crisis, and death in situations that necessitate increased availability of cortisol. Under conditions of stress (serious infection, trauma, surgery), all children who are at risk for hypothalamic-pituitary-adrenal axis suppression require supplemental GCs.

Intravenous pulse glucocorticoid therapy

As stated above, high-dose "pulse" intravenous GC therapy is sometimes used to treat the most severe or acute manifestations of systemic connective tissue diseases, such as JSLE, JDM, and vasculitis. Another potential indication is the management of refractory systemic features of systemic-onset JIA. Although no controlled trials have been reported in children, this treatment modality has become increasingly popular over the years in paediatric rheumatology practice (18). This approach is aimed to achieve an immediate, profound anti-inflammatory effect and to lessen toxicity associated with long-term continuous therapy in moderate to high daily doses. The drug of choice has been methylprednisolone, given in doses of 10 to 30 mg/kg per pulse up to a maximum of 1 g, administered according to a variety of protocols: a pulse each day for 3 to 5 days, alternate-day pulses for 3 doses, or a single administration repeated as clinical events warrant.

In the clinical setting, the calculated drug dose is usually added to 100 ml. 5% dextrose in water and infused over 1–3 hours. Patient monitoring includes assessment of temperature, pulse rate, respiratory rate, and blood pressure before beginning infusion. Pulse rate and blood pressure should then be checked every 15 minutes for the first hour and then every 30 minutes. Infusions should be slowed or discontinued if there are any significant changes in blood pressure or pulse rate.

The most commonly reported (10% of patients) short-term adverse effect of intravenous GC pulse therapy in children is abnormal behaviour, with altered mood, hyperactivity, psychotic symptoms, disorientation, and sleep disturbances. Other side effects include headache, abdominal discomfort, vomiting, hives, hypertension, dizziness, lethargy, hypotension, tachycardia, and hyperglycemia. Little information is available about whether this procedure is associated with an increased risk for long-term side effects, such as osteoporosis or avascular necrosis of bone.

Intra-articular corticosteroid

Intra-articular corticosteroid (IAC) injections are widely used in the management of children with juvenile idiopathic arthritis (JIA) to induce rapid relief of inflammation symptoms and functional improvement, and to obviate the need for regular systemic therapy (19-21). However, despite long use in paediatric rheumatology practice, much of the evidence supporting IAC therapy remains anedoctal or based on open, non-controlled studies. Furthermore, wide disparities likely exist in the indications for IACs, injection technique, and protocols for sedation and post-injection management across different settings.

Although potentially effective on all subtypes of JIA, IAC injections are used most frequently to treat oligoarthritis. IAC therapy may prevent some important musculo-skeletal abnormalities in this JIA subset, such as flexion contractures, valgus deformity and leg-length discrepancy. Furthermore, IAC therapy has been proved to facilitate discontinuation of oral medications, resolve Baker's cysts, and improve tenosynovitis (22).

The strategy of performing multiple IAC injections is used by some paediatric rheumatologists in children with polyarticular JIA to induce prompt remission of synovitis, while simultaneously initiating therapy with disease-modifying drugs (DMARD) and/or biologic agent. This approach is regarded as an alternative to systemic corticosteroids to pursue the so-called "bridge" effect, that is, to achieve a quick control of inflammatory symptoms while awaiting the full therapeutic effect of a DMARD or biologic medication.

The duration of response to IACs is dependent on the corticosteroid used, with less soluble preparations providing a longer duration of response. Triamcinolone hexacetonide (TH), the least soluble agent, is universally recognised among paediatric rheumatologists as the medication of choice for intra-articular administration in JIA. The corticosteroid preparations and dosage regimen of IAC injections currently used in the authors' center is reported in Table I.

In the post-injection period, the authors' recommendation is to avoid weight bearing for the first 24 hours (72 hours in case of injection in the hip) and to avoid high-impact physical activity in the 24 to 72 hours after a joint injection. In case of relapse of synovitis, reinjection is commonly performed. Although there are no established guidelines for this practice, most rheumatologists will limit the frequency of reinjections to 3 times per year, with repeated procedures being performed at least 3 months apart.

The outcome and predictive variables of single and multiple IAC injections have been investigated recently in 440 children with JIA (23). The cumulative probability of remission of synovitis for patients injected in 1, 2 or 3 or more joints was 70, 45 and 44%, respectively, at 1 year; 61, 32 and 30%, respectively, at 2 years; and 37, 22 and 19%, respectively, at 3 years. Patients with systemic arthritis developed a synovitis flare more frequently and precociously than did patients with polyarthritis and oligoarthritis. The risk of synovitis flare was higher in patients who had positive CRP, negative ANA and were injected in the ankle.

The most common adverse effect of IAC injections is subcutaneous atrophic skin changes at the site of injection, particularly of small joints such as wrist and ankles in young children. It is caused by extravasation of the injected

Table I. Type and dose of corticosteroids currently used for intra-articular corticosteroid injections at the authors' centre.

Joint	Corticosteroid	Dose
Shoulder	TH	1 mg/kg (max 40 mg)
Elbow	TH	0.75 mg/kg (max 30 mg)
Wrist	TH	0.25–0.5 mg/kg § (max 20 mg)
Hand metacarpophalangeal and interphalangeal	MP	5-10 mg §
Hip	TH	1 mg/kg (max 40 mg)
Knee	TH	1 mg/kg (max 40 mg)
Ankle	TH	0.75 mg/kg (max 30 mg)
Subtalar and intertarsal	MP	20–40 mg §
Foot metatarsophalangeal and interphalangeal	MP	5–10 mg §
Tendon sheats	MP	20–40 mg §

TH: triamcinolone hexacetonide; MP: methylprednisolone acetate. § Depending on the child's size. Adapted from Scott C. *et al*. (ref. 21).

medication from the joint space. Subcutaneous atrophy may resolve with time in most patients, but persists in some. The risk of this complication is minimised by following a careful injection technique, ensuring accuracy of needle placement in the joint space, and clearing the needle track with injection of saline or local anesthetic as the needle is withdrawn from the joint. No detrimental effect of IAC on intra-articular cartilage or statural growth has been observed (24).

The potential role of IAC injections in the hip in causing avascular necrosis of the femoral head is unclear. Reported studies suggest that the risk is small and is probably increased by the simultaneous administration of systemic GCs (25, 26). Although systemic absorption of corticosteroids has been found to cause significant adrenal suppression and transient clinical manifestations ranging from minor cosmetic changes to Cushingoid features, it is not associated with long-term adverse effects and is short-lived.

Another known complication of IAC injections is the development of periarticular calcifications. The majority of these abnormalities are asymptomatic and are detected coincidentally on radiological follow-up. A report of septic arthritis of the ankle 48 hours after an IAC injection in a knee in a child with respiratory infection suggests that the procedure should be postponed if the child has signs of an intercurrent infection (27). A TB infection should be excluded before the IAC injection.

Injected corticosteroids may cause a crystal-induced synovitis, which may present with post-injection erythema and pain. This is thought to result from phagocytosis of corticosteroid crystals in the joint, leading to the release of inflammatory mediators (28). These symptoms usually subside spontaneously or with local ice application within a few days. Acute anaphylaxis following IAC injection has been described in adult patients, but has never been reported in children. Diabetic children may require a temporary increase in insulin requirements.

Conclusion

GCs remain an important therapeutic option for children with rheumatic diseases. Administration of these drug enables a quick and effective control of the systemic inflammatory process and helps prevent the resulting damage to organs and systems. The newer modalities of GC administration, namely the intravenous methylprednisolone pulses, may lead to achieve an immediate, profound anti-inflammatory effect and to lessen toxicity associated with long-term continuous therapy in moderate to high daily doses. Intra-articular corticosteroid (IAC) injection is a safe and rapidly effective treatment for synovitis in children with JIA. Use of GCs is associated with potentially deleterious adverse effects, some of which can be irreversible. This highlights the need for judicious use of these medications and careful monitoring of their side effects.

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