Corticosteroids in the Treatment of Childhood Rheumatic Diseases: A Historical Review

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Corticosteroids, in one form or another, are major components of the armamentarium the pediatric rheumatologist uses to treat many of the rheumatic diseases of childhood. Their introduction in 1949 revolutionized the pharmacologic care of adults with rheumatoid arthritis (RA), and soon thereafter, their use in observational studies of children with chronic arthritis and other rheumatic diseases was reported. That they continue to have a prominent place in treating children with rheumatic diseases is a reflection of their role as potent suppressors of inflammation (notwithstanding their significant side effects) and the fact that, until quite recently, there was little other effective treatment to offer children aside from symptomatic relief with nonsteroidal anti-inflammatory drugs. The early application of corticosteroids to the treatment of childhood rheumatic diseases is reviewed in this chapter.

The Origins of Corticosteroid Therapy

Hench and Kendall described the remarkable effects of cortisone on the inflammation of RA in a detailed account published in the *Mayo Clinic Proceedings* in 1949 [1]. For their work, Hench, a rheumatologist; Kendall, a biochemist, both at the Mayo Clinic in Rochester, Minnesota; and Reichstein, a steroid chemist in Basel, Switzerland, received the Nobel Prize in Medicine in 1950 [2].

Several apparently unrelated clinical observations led Hench to collaborate with Kendall on evaluation of the therapeutic effect of adrenocortical hormones in RA. Hench had studied the remissions in RA induced by pregnancy [3] and jaundice

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[4] and postulated that a naturally occurring factor common to both could be responsible for remissions in joint disease. Of interest, George Frederic Still had also noted marked improvement in children with chronic arthritis following "catarrhal jaundice" [5]. (Crocker and colleagues more recently argued that it is changes in lipids, rather than cortisone concentrations, occurring in both pregnancy and jaundice that are responsible for the remission in inflammatory disease [6].) Hench was aware of the brief remissions in RA induced by surgery, a procedure known to be accompanied by stimulation of the adrenal glands, and began collaborations with Kendall, who was actively investigating the many steroids found in the adrenal cortex. With the purification of sufficient quantities of one steroid, "compound E," from bovine bile, it was administered to a young woman with severe RA. The result, known to all rheumatologists, was that the patient, who had been unable to walk, resumed ambulation within days of receiving the drug. Her recovery prompted the use of compound E in 14 other patients with RA, with similar dramatic effects. Compound E was renamed cortisone. The early studies of the use of cortisone in adults with RA are thoroughly reviewed by Lundberg and colleagues [7].

Corticosteroids in the Treatment of Childhood Arthritis

Elkinton and colleagues [8] (1949) reported the use of adrenocorticotropic hormone (ACTH) in two children with juvenile rheumatoid arthritis (JRA). The clinical response was prompt, but fever and arthritis returned when the drug was discontinued. Bergman and Kinberger [9] may have been the first (1950) to report the use of a corticosteroid (desoxycorticosterone acetate) in the treatment of a child with chronic arthritis [9]. In 1951, Wolman described the striking response to oral cortisone in children with chronic arthritis, rheumatic fever, and nephrotic syndrome [10]. This detailed report also documented the disease recurrence after cortisone was discontinued, often because of unavailability of the drug.

In 1952, Bunim et al. [11] described the effects of cortisone in 31 children with active rheumatic carditis and seven children with JRA. The manifestations of active rheumatic fever responded within a few days, but relapses were noted when the cortisone dose was reduced in some patients. Barkin et al. had described the outcome in 51 children with JRA in the pre-corticosteroid era [12]; 11 of 51 patients died (eight from the effects of amyloidosis), and seven were confined to bed or wheelchair. Against this background, the effect of corticosteroids reported by Bunim et al. was dramatic: three of five children who were bed-ridden prior to treatment with cortisone and had arthritis for less than 1 year regained full joint function within 2 months; the remaining two had had arthritis for longer periods, but became ambulatory after 2 and 24 months, respectively. The authors noted that some changes (erosions, muscle wasting) were not reversible, and that relapse of active arthritis following cessation of cortisone was frequent.

This encouraging study was followed by others with inconsistent conclusions. A randomized prospective trial compared aspirin ($n=12$) and cortisone ($n=13$) in

children with "Still's disease" [13]. Patients in each group were treated over a period of 1 year in blocks of 12 weeks followed by a 1-week period off drugs. Cortisone was given in a dose of 300 mg on the first day with a taper to 100 mg/day by 1 week (equivalent to 20 mg of prednisone or prednisolone). Aspirin was given in a dose of 6 g/day for the first week, then 2 g/day for the second week with subsequent variation in the dose between 2 and 6 g depending on clinical state. Later in the study the interrupted treatment courses were abandoned in favor of continuous treatment. At 1 year, overall improvement in both groups was similar. Glyn has written an interesting first-hand account of the early cortisone versus aspirin trials in adults in the United Kingdom [14].

Harnagel reported somewhat discouraging results in a case series of 15 children with JRA, 80 % of whom had symptomatic improvement, but only 40 % of whom had objective improvement while taking prednisone or prednisolone [15]. Harnagel noted, also, that there were frequent side effects: "moon face," acne, striae, psychologic changes, diabetes mellitus. Lindbjerg [16] reported similarly unimpressive results in a retrospective review of children with JRA, noting that those treated with corticosteroids (usually ACTH sometimes followed by cortisone or prednisone) were no better than those treated with gold and aspirin. These early, somewhat discouraging results of corticosteroid treatment in children are not entirely explicable, although dose and duration of therapy, disease severity and type, study design, and therapeutic goal may have played a role in some instances. By contrast, Schlesinger and colleagues [17] reported the disease course and treatment in 100 children with Still's disease, and noted the marked benefit associated with cortisone treatment.

Although the literature does not document other randomized controlled trials of cortisone, ACTH, or other forms of glucocorticoids in children with chronic arthritis, these drugs became widely used. No formal dose-finding studies were reported, and regimens of administration were based on individual clinicians' experience. In the United Kingdom, in particular, alternate-day prednisone was widely used. In other parts of the world, prednisone was often administered daily, or multiple times each day. Prednisolone (in Europe) and prednisone (in North America) became the glucocorticoid drug of choice for oral administration. Prednisone is rapidly converted to its active form, prednisolone, by the liver, and in the absence of severe liver disease, the relative anti-inflammatory potency of these two drugs is equivalent.

Initially, both ACTH and cortisone were used. There was no consistent evidence that endogenous ACTH production or adrenal gland function was diminished in patients with arthritis, and it was clear that pharmacologic rather than physiologic doses of cortisone were required to suppress joint inflammation. It seemed logical to use the effective agent (cortisone) rather than ACTH, but concern about major side effects (particularly growth suppression and osteoporosis) prompted studies comparing the effects of ACTH versus prednisone on the frequency and severity of these complications. Zutshi et al. [18] concluded that ACTH may be superior to prednisolone in this regard. Ansell and Bywaters [19] reported the good effect of ACTH in six children with Still's disease and one with systemic lupus erythematosus (SLE), using a daily intramuscular administration, intermittent muscular administration, or intermittent intravenous administration.

In spite of these early observations, ACTH is no longer used to treated inflammatory disease in children for many reasons: It required intramuscular injection, it was not always readily available, was poorly standardized [18], and, in recent years, has become very expensive.

Intra-articular injection of corticosteroid has a long history in adult rheumatology [20]. However, there was concern that intra-articular corticosteroids might be harmful to the immature cartilage and it was not until the mid-1980s that injection of triamcinolone hexacetonide into inflamed joints in children with juvenile idiopathic arthritis (JIA) was demonstrated to be effective [21] and safe [22]. The superiority of triamcinolone hexacetonide has been demonstrated [23], although triamcinolone acetonide is still widely used, and for small joint or tendon sheath injections cortisone may be preferred.

For active anterior uveitis, topical corticosteroid, reported by Smiley and colleagues in 1957 [24], in an approach that remains essentially unchanged today, is usual first-line therapy, although it is frequently ineffective and it is recommended that the duration of its use be limited because of the risk of cataract and increased intraocular pressure [25]. Subconjunctival steroid injections are occasionally used.

Corticosteroids in Treatment of Connective Tissue Diseases of Childhood

The potent anti-inflammatory effects of corticosteroids in children with juvenile arthritis led to their use in children with other chronic rheumatic diseases.

Elkinton and colleagues reported (1949) the effective use of ACTH in a 6-year-old boy with dermatomyositis. Thorn and colleagues described the use of ACTH in two children with dermatomyositis [26] in 1950. Wedgwood and colleagues later evaluated the effectiveness of ACTH in these patients as equivocal [27]. Bitnum et al. noted the use of ACTH or cortisone in nine children with dermatomyositis [28]. Wedgwood et al. described the treatment of 11 children with dermatomyositis with ACTH or cortisone [27]. Seven patients received prolonged courses of ACTH (sometimes together with testosterone), and four patients received cortisone. In children with active disease, the immediate effects were very promising, but the authors noted that two of the children died subsequently. Hill and Wood [29] emphasized the import role of corticosteroids in the successful outcome of juvenile dermatomyositis. Sullivan et al. [30] documented the benefit of high-dose prednisone given up to four times daily in children with severe dermatomyositis. Prednisone remains the mainstay of the initial treatment of this disease, coupled with methotrexate.

A few months after the publication of the seminal paper by Hench et al., Harvey and colleagues [31] reported the dramatic benefit of ACTH on four adults with SLE. The first large series of children ($n = 37$) with SLE who were treated with prednisone was published by Cook et al. in 1960 [32]. Jacobs described a similar group of children with SLE in 1963, some of whom had anticonvulsant-induced disease, and noted the beneficial effect of prednisone in both groups [33]. Corticosteroids are

now an essential component of the treatment of almost every child with SLE. By contrast, systemic scleroderma is corticosteroid unresponsive, although morphea or localized scleroderma is most often treated with a combination of prednisone (for a period of a few months) and methotrexate (for a longer period) [34].

Case reports and small case series of children with polyarteritis [35] and Wegener's granulomatosis [36] were reported in 1950 and 1979, respectively, and with one exception, corticosteroid treatment of systemic vasculitis became the standard of care. The controversy surrounding the use of corticosteroids in Kawasaki disease (KD), the exception, is not entirely settled. Kato et al. [37] compared the frequency of coronary artery disease in five groups of children with KD each treated with a different regimen. He and his colleagues concluded that children treated with prednisone had the highest frequency of coronary artery disease. This study had important design flaws, but had the effect of making corticosteroid therapy of KD contraindicated. In a subsequent study, Kijima and colleagues [38] demonstrated that in patients with KD and with dilated coronary arteries, intravenous pulse methylprednisolone (30 mg/kg/days × 3 days) prevented the worsening of the change or reversed the changes altogether. Corticosteroids are now considered to be second-line therapy in children who are resistant to treatment with intravenous immunoglobulin [39], and their place as first-line therapy is being investigated [40, 41].

Pursuit of Efficacy with Minimal Toxicity

Most rheumatic diseases are chronic, and require therapy over a period of years. Corticosteroids, while remarkably effective suppressors of inflammation, are the cause of considerable morbidity when given for more than a few weeks at high doses. Attempts to minimize toxicity have taken two paths. First, administration of the lowest possible effective dose for the shortest possible period is accepted practice. Administration of the drugs on an intermittent (i.e., alternate day) basis definitely diminishes side effects, but may not be as effective, especially in active or severe disease. Administration of high-dose intravenous "pulse" methylprednisolone is often favored in systemic connective tissue diseases because it minimizes the amount and duration of daily oral therapy. Cole and colleagues [42] reported the successful use of intravenous "pulse" corticosteroids in the treatment of life-threatening glomerulonephritis in eight patients, two of whom had Henoch–Schönlein purpura. Levinsky et al. [43] described the effectiveness of high-dose intravenous methylprednisolone in two patients (age 18 and 11 years) with SLE. Miller reported the successful use of large doses of corticosteroids in children with rheumatic diseases [44]. In this study, children with polyarticular JRA ($n=4$), systemic JRA ($n=5$), dermatomyositis ($n=4$), SLE ($n=2$), and other disorders received either intravenous hydrocortisone (500 mg q6h × 4 doses), or intravenous methylprednisolone (30 mg/kg) with good effect and few side effects over a follow-up period of up to 3 years. Intravenous methylprednisolone pulse therapy is now widely used in the treatment of a variety of childhood rheumatic diseases, especially systemic JIA, SLE, dermatomyositis, and many of the vasculitides.

Use of local therapy (e.g., intra-articular corticosteroids) rather than systemic corticosteroids can also minimize systemic toxicity (growth suppression, weight gain, etc.).

The second approach has been to develop corticosteroids with less toxicity. Deflazacort, a derivative of prednisolone, has been alleged to be superior to prednisone or prednisolone with regard to weight gain, growth in height, and bone mineralization, while having an equivalent anti-inflammatory effect at 6 mg compared with prednisolone at 5 mg (reviewed by Joshi and Rajeshwari) [45]. A prospective randomized trial in children with JIA confirmed a modest benefit of alternate-day low-dose deflazacort over alternate-day low-dose prednisolone with respect to bone mineralization [46]. The published literature describing the use of deflazacort in children with rheumatic diseases is very limited; it is not universally available, and its current use appears to be restricted primarily to the treatment of children with Duchenne muscular dystrophy.

Summary

The role of corticosteroids today in the management of childhood rheumatic diseases is well established. Toxicity remains a major concern and is related primarily to drug dose, frequency of drug administration, and duration of therapy. As a result, corticosteroids should be administered in the lowest effective dose, given as infrequently as possible, for as short a time period as possible. In the management of JIA, prednisone is ordinarily restricted to be used as a "bridge" while awaiting the effect of agents such as methotrexate, and in the acute management of active systemic features of systemic JIA [47]. Intra-articular triamcinolone hexacetonide has an important place in the management of arthritis. Topical corticosteroids retain a vital role in the management of uveitis. Systemic corticosteroids (oral prednisone and/or prednisolone or intravenous "pulse" methylprednisolone) are essential components of the management of SLE, dermatomyositis, and the vasculitides. The benefit of one drug (deflazacort) over others with respect to toxicity is doubtful. With the advent of the newer disease-modifying anti-inflammatory drugs and the biologics, toxicity is a lesser problem because long-term corticosteroid use is much less frequent.

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