Rheumatology International (2019) 39:13–27
https://doi.org/10.1007/s00296-018-4168-0

Rheumatology
INTERNATIONAL

REVIEW

Glucocorticoid treatment in juvenile idiopathic arthritis

Ezgi Deniz Batu[1]

Received: 28 August 2018 / Accepted: 26 September 2018 / Published online: 1 October 2018

Abstract
Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of joints in childhood. Glucocorticoids are being used in JIA treatment effectively for decades. Although systemic glucocorticoid use decreased with the introduction of biologic drugs, intraarticular glucocorticoid injections (IAGI) with nonsteroidal anti-inflammatory drugs and non-biologic disease modifying anti-rheumatic drugs (DMARDs) still remain the primary treatment in JIA, especially in oligoarticular subcategory. Systemic glucocorticoids are used mainly for severe JIA-associated complications such as macrophage activation syndrome (MAS), myocarditis, pericarditis, pleuritis, peritonitis, and severe anemia; as bridging therapy while waiting for the full therapeutic effect of DMARDs; and in certain occasions for patients with severe refractory uveitis. Since glucocorticoid administration is associated with many adverse events, it is important to use glucocorticoids in an optimum way balancing the risks and benefits. The aim of this review is to summarize the current knowledge on glucocorticoid treatment in JIA. A comprehensive literature search was conducted utilizing the Cochrane Library and MEDLINE/PubMed databases. The main topics include mechanism of action, dose, duration, adverse events, vaccination during glucocorticoid treatment, the place of glucocorticoids in JIA treatment guidelines and consensus treatment plans, glucocorticoid use in JIA-associated uveitis, MAS, and IAGI. Data from the literature provide guidance on how to use glucocorticoids in JIA treatment especially for IAGI and systemic use in systemic JIA and MAS. However, there is lack of evidence and need for prospective randomized studies in most parts including the indications in different JIA subcategories, optimum dose/route of administration/duration of treatment, and tapering strategies.

Keywords Juvenile idiopathic arthritis · Glucocorticoid · Corticosteroid · Intraarticular glucocorticoid injection

Introduction

Juvenile idiopathic arthritis (JIA) is a chronic rheumatic disease characterized by arthritis of unknown etiology that persists for at least 6 weeks with onset before the 16th birthday [1]. JIA is classified into seven subcategories by the International League of Associations for Rheumatology (ILAR) as systemic arthritis, oligoarthritis, rheumatoid factor (RF) negative polyarthritis, RF positive polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis [1].

First line of treatment in JIA usually consists of nonsteroidal anti-inflammatory drugs (NSAIDs) and intraarticular glucocorticoid injections (IAGIs). These interventions still form the mainstay of therapy especially in oligoarticular JIA [2]. The second-line agents are non-biologic disease-modifying anti-rheumatic drugs (DMARDs). Methotrexate is the most widely used non-biologic DMARD in JIA patients [3]. The use of systemic glucocorticoids in JIA is currently limited with bridging therapy (while waiting for the therapeutic effect of DMARDs) and special indications such as macrophage activation syndrome (MAS) [4]. The introduction of biologic drugs to treatment during the last two decades has greatly improved the outcome and reduced the use of systemic glucocorticoids in patients with JIA.

Glucocorticoids are the most commonly used anti-inflammatory immunosuppressive drugs. Philip Hench, Tadeusz Reichstein, and Edward Calvin Kendall got the Nobel Prize in Physiology and Medicine in 1950 for discovering the important anti-inflammatory effects of corticosteroids. After that time, the use of glucocorticoids in the treatment of inflammatory diseases has increased tremendously. Systemic

✉ Ezgi Deniz Batu
ezgidenizbatu@yahoo.com

[1] Department of Pediatrics, Division of Rheumatology, Ankara Training and Research Hospital, University of Health Sciences, Ankara 06100, Turkey

glucocorticoid use is still common in JIA especially in systemic subcategory.

Around 1200 JIA patients have been recruited from 49 clinical sites in the recent CARRA (The Childhood Arthritis and Rheumatology Research Alliance) registry and nearly half of these patients have used systemic glucocorticoid treatment in the follow-up [5]. The probability of initiating systemic glucocorticoids in the first 6 months of disease diagnosis is highest among patients with systemic JIA when compared to those with other JIA subcategories [6]. According to the German National Pediatric Rheumatology Database between 2000 and 2013, one-third of systemic JIA patients were still being treated with systemic glucocorticoids at the 3-year follow-up and growth retardation was associated with ongoing systemic glucocorticoid treatment in addition to the persistently high disease activity [7]. In another study, including Canadian children with JIA between 2005 and 2010, 85.5% of systemic JIA patients used systemic glucocorticoids and these patients had an estimated 3-year cumulative incidence of 9.3% for new-onset short stature and 34.4% for obesity [8]. Thus, it is important to examine glucocorticoid strategies and glucocorticoid-related adverse events in JIA. It is noteworthy that the physicians increasingly prefer other therapies for long-term disease control since long-term systemic glucocorticoid use is associated with severe side effects. Besides, controlled studies are scarce on systemic glucocorticoid use in JIA.

The aim of this review is to overview the current data on glucocorticoid use in JIA treatment.

Search strategy

The Cochrane Library and MEDLINE/PubMed databases were searched (from database inception to 15 July 2018) according to the published guidance on narrative reviews [9] by entering the following keywords: ("juvenile idiopathic arthritis" OR "juvenile chronic arthritis" OR "juvenile rheumatoid arthritis") AND ("glucocorticoid" OR "corticosteroid" OR "steroid" OR "prednisone" OR "prednisolone" OR "dexamethasone" OR "methylprednisolone" OR "triamcinolone hexacetonide" OR "triamcinolone acetonide" OR "methylprednisolone acetate"). Case reports, original research articles, and review articles with a focus on glucocorticoid treatment in JIA were analyzed. The search was restricted to English articles.

Mechanism of action

Corticosteroids are synthetic analogs of natural steroids [10]. These drugs have both mineralocorticoid and glucocorticoid properties. Mineralocorticoids are important for electrolyte and water balance while glucocorticoids have anti-inflammatory, immunosuppressive, anti-proliferative, and vasoconstrictive effects [10]. Glucocorticoids exert their anti-inflammatory effects through their glucocorticoid receptors [11]. They have both genomic and rapid, non-genomic anti-inflammatory effects. When glucocorticoids bind to their receptors, the receptors translocate to the nucleus and repress the transcription of proinflammatory genes while activating the transcription of anti-inflammatory genes [11–13]. Non-genomic effects occur via interaction of glucocorticoid receptors with kinases which affects inflammatory signaling pathways [14].

The term "glucocorticoid" is preferred throughout this text in accordance with the EULAR (European League Against Rheumatism) recommendations since the anti-inflammation is the desired effect in JIA treatment [15].

Glucocorticoid dose and duration of treatment

According to the EULAR definitions, low dose is $\leq$7.5 mg, medium dose > 7.5 but $\leq$30 mg, high dose > 30 but $\leq$100 mg, and very high dose is > 100 mg prednisolone or equivalent daily [15]. Pulse therapy is defined as $\geq$250 mg prednisolone or equivalent a day for one or a few days. However, this terminology could not be applied to the pediatric patients, since the dose is calibrated according to the body weight in children with JIA. In vaccination recommendations of EULAR, low-dose glucocorticoids were defined as < 0.5–2 mg/kg/day and high dose as $\geq$2 mg/kg/day or a total of $\geq$20 mg/day for 2 weeks or more [16]. The approximate equivalent doses (mg) for commonly used glucocorticoids in JIA treatment are as follows: 5 for prednisone or prednisolone, 4 for methylprednisolone, and 0.75 for dexamethasone [17]. There is no consensus about the nomenclature of the duration of glucocorticoid treatment; however, usually < 3 months is considered short-term [18]. In EULAR publication about long-term glucocorticoid use, long-term refers to (3–) 6 months or more [19].

There are no evidence-based data for exact dose and duration of systemic glucocorticoid treatment in JIA. For severe indications, such as MAS, myocarditis, pleuritis, pericarditis, peritonitis, and severe anemia, high dose pulse intravenous (IV) methylprednisolone (10–30 mg/kg/day, maximum 1 g/day, for 1–3 days) could be followed by oral prednisolone (or equivalent) at a dose of 1–2 mg/kg/day (maximum 60 mg/day) [20, 21]. When glucocorticoids are given orally, the bioavailability is estimated to be around 82% in comparison with intravenous route [22]. However, there is no study comparing the efficacy of different glucocorticoid doses when given orally or intravenously in JIA. The duration of glucocorticoid treatment varies according to the time

of improvement in clinical and laboratory parameters. Short course of lower dose glucocorticoids (usually ≤ 0.5 mg/kg/day oral prednisolone or equivalent for ≤ 2 weeks) could be used for bridging therapy while waiting for full therapeutic effect of DMARDs [20, 21]. When to start tapering glucocorticoid therapy is another area of debate. Wide inter-study variations exist in the literature. In 2012, an algorithm was developed for glucocorticoid management in systemic JIA rilonacept trial [23]. Based on consensus, the authors identified criteria for tapering glucocorticoids as the absence of fever ≥ 3 days in the previous week, the absence of poor physical functioning, and the presence of seven laboratory criteria (ferritin ≤ 2500 µg/l; platelets ≤ 800,000/ml, fibrinogen > lower limit of normal, INR ≤ 1.2, white blood cell count > lower limit of normal, hemoglobin ≥ 7.5 g/dl). The rate of tapering was determined as 10% of the current daily dose every two weeks [23]. Glucocorticoid tapering strategies in CARRA consensus treatment plans (CTPs) have been discussed below.

Glucocorticoids in treatment guidelines and consensus treatment plans of juvenile idiopathic arthritis

The place of systemic glucocorticoids in American College of Rheumatology (ACR) guidelines and CARRA CTPs is summarized in Table 1. General outline on glucocorticoid use in JIA is presented in Fig. 1.

American College of Rheumatology (ACR) 2011 guideline

Intraarticular glucocorticoid injection and systemic glucocorticoids for treatment of only systemic features of JIA were included in 2011 ACR recommendations; systemic glucocorticoids for treatment of synovitis were not included because of lack of evidence in the literature [24]. However, these recommendations were criticized for excluding systemic glucocorticoid treatment for arthritis [25].

Table 1 Systemic glucocorticoids in American College of Rheumatology (ACR) guidelines and the Childhood Arthritis and Rheumatology Research Alliance (CARRA) consensus treatment plans (CTPs)

Recommendations/CTPs	Reference number	Subcategory of JIA	Other prerequisites	Tapering
ACR 2011 recommendations	[24]	SJIA with active systemic features without active arthritis	Active fever and PGA ≥ 7 OR Active fever after NSAID trial	NA
ACR 2013 recommendations	[26]	SJIA with significant systemic features and varying degree of synovitis	PGA ≥ 5 or PGA < 5 and AJC > 4 OR PGA ≥ 5 or PGA < 5 and AJC > 0 after NSAID trial fails Optional adjunct therapy	NA
		SJIA with features concerning for MAS	–	NA
CARRA CTPs	[28]	SJIA	Glucocorticoid-only CTP	If not tapered by ≥ 50% of SD by 3 months, switch CTPs
CARRA CTPs	[29]	PolyJIA	Optional adjunct therapy	Four strategies SD 0.2 mg/kg (max 20 mg), taper at 2 weeks SD 0.5 mg/kg (max 30 mg) taper at 1 month SD 1 mg/kg (max 60 mg), taper at 1 month SD 1 mg/kg (max 60 mg), taper at 3 months

ACR American College of Rheumatology, *AJC* active joint count, *CARRA* The Childhood Arthritis and Rheumatology Research Alliance, *CTP* consensus treatment plan, *JIA* juvenile idiopathic arthritis, *NA* not addressed, *PGA* physician global assessment, *SD* starting dose, *SJIA* systemic JIA

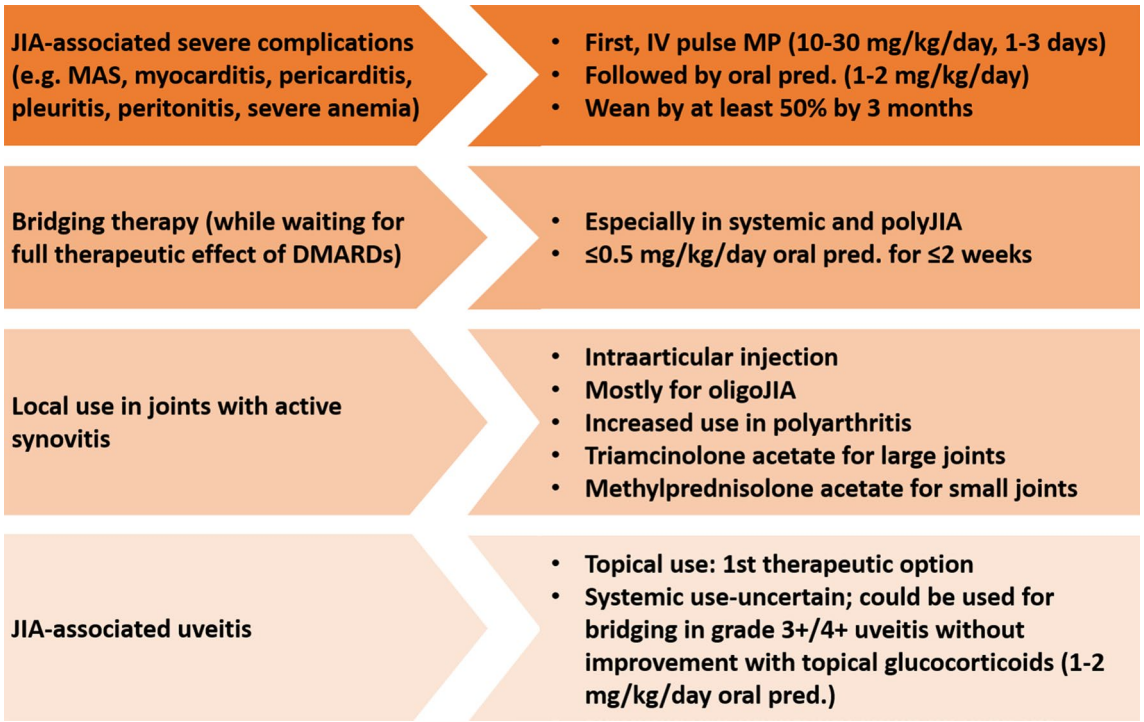

Fig. 1 General outline for glucocorticoid use in juvenile idiopathic arthritis (*DMARD* disease-modifying anti-rheumatic drugs, *JIA* juvenile idiopathic arthritis, *MAS* macrophage activation syndrome, *MP* methylprednisolone, *pred*. prednisolone)

IAGIs are recommended for treatment of active arthritis in all types of JIA regardless of the systemic therapy. It could be repeated at any time after 4 months, as needed. If the clinical improvement with IAGI lasts less than 4 months, escalation of systemic therapy could be considered.

Systemic glucocorticoids are recommended as the initial therapy in patients from the group of "systemic arthritis with active systemic features and without active arthritis", if the patient has active fever and a physician global assessment (PGA) of overall disease activity of ≥ 7 of 10. It is recommended for the treatment of all patients from the aforementioned group with active fever after a 2-week NSAID trial.

ACR 2013 guideline

In 2013 update of ACR recommendations, systemic JIA was evaluated in three sub-phenotypes: significant systemic features and varying degrees of synovitis, significant arthritis and no significant systemic features, and features concerning for MAS [26].

IAGI was recommended at any time in the follow-up irrespective of the systemic treatment. It was also recommended as an initial sole therapy option for patients with active joint count (AJC) ≤ 4 from group of "without active systemic features and with varying degrees of synovitis". If the patient has AJC > 4, the use of IAGI as the only therapeutic option was uncertain.

Systemic glucocorticoid monotherapy is recommended as a treatment option for patients with "significant systemic features and varying degrees of synovitis" if PGA < 5 and AJC > 4 or PGA ≥ 5 irrespective of the AJC. It was also recommended as a secondary treatment option after failed NSAID for patients with PGA < 5 and AJC > 0 and for patients with PGA ≥ 5 irrespective of AJC. Systemic glucocorticoid treatment was recommended also as an adjunct therapy at any time in patients with active systemic features. The maximum duration for systemic glucocorticoid therapy was defined as 1 month.

For the patients who have "systemic JIA with features concerning for MAS", systemic glucocorticoid monotherapy was recommended as an initial therapeutic option; however, the treatment duration should be < 2 weeks.

The dose, tapering strategies, and minimum duration of glucocorticoid treatment were not addressed in ACR recommendations.

In 2016, the Canadian Rheumatology Association Pediatric Committee reported a position statement mainly endorsing the ACR recommendations for JIA treatment [27].

The Childhood Arthritis and Rheumatology Research Alliance (CARRA) consensus treatment plans (CTPs)

The Childhood Arthritis and Rheumatology Research Alliance (CARRA) developed four CTPs for the first 9 months

of new-onset systemic JIA treatment: glucocorticoid plan, methotrexate plan, interleukin 1 inhibitor plan, and tocilizumab plan [28, 29].

Glucocorticoid plan starts with 1 mg/kg (maximum 60 mg) daily prednisone with optional IV methylprednisolone pulses (30 mg/kg, maximum 1 g, daily) for three days. After 1–2 weeks, if improved, prednisone could be tapered. If the situation is unchanged, the same dose prednisone could be continued. And if worsened, prednisone dose could be increased to 2 mg/kg (maximum 100 mg) with optional IV methylprednisolone pulses. If glucocorticoids could not be weaned by at least 50% of the starting dose by 3 months; switching CTPs is recommended.

The methotrexate and biologic drug plans allow for addition of glucocorticoids dosed according to the glucocorticoid-only plan.

In 2014, CARRA published treatment recommendations for new-onset polyarticular JIA [30]. Of note, polyarticular JIA was defined as all JIA with > 4 joints involved throughout the disease; including both polyarticular and extended oligoarticular JIA subcategories of ILAR [1, 30]. The CTPs are step-up plan (biologic DMARD follows non-biologic DMARD trial), early combination plan (non-biologic and biologic DMARD combined), and biologic only plan. In these treatment plans, addition of systemic glucocorticoids and IAGI are optional at any time. In the case of systemic glucocorticoid treatment, it is recommended to use the lowest effective dose, to taper as quickly as possible, and to discontinue by 3 months, if possible.

Glucocorticoid tapering strategies are defined in these recommendations in four options: (1) starting dose (SD) 0.2 mg/kg (maximum 20 mg) with rapid taper in 2 weeks; (2) SD 0.5 mg/kg (maximum 30 mg) with fast taper in 1 month; (3) SD 1 mg/kg (maximum 60 mg) with fast taper in 1 month; and (4) SD 1 mg/kg (maximum 60 mg) with slow taper in 3 months. The steps of tapering are detailed in the recommendations [30].

In a pilot study comparing the CARRA systemic JIA CTPs, Kimuro et al. reported that clinical inactive disease off-glucocorticoids was achieved more frequently by patients who received a biologic CTP than those receiving a non-biologic CTP (glucocorticoids alone or methotrexate ± glucocorticoids) (50% vs 0%, respectively; $p = 0.014$) [31]. A multicenter, prospective, non-randomized study called "FiRst-time Options for Systemic JIA Treatment" (FROST) is underway which will provide the first prospective comparison of CARRA CTPs including "glucocorticoid alone" CTP, performed in a real-world setting [32].

German guidelines

In 2012, German Society for Pediatric Rheumatology published guidelines for JIA treatment [33]. They recommended systemic glucocorticoid use for the treatment of children/adolescents with systemic JIA, organ manifestations of JIA such as uveitis and pericardial effusion, sero-positive polyarticular JIA, and for bridging time until DMARDs become effective. It is important to note that they recommended against long-term use of systemic glucocorticoids. IAGI is recommended noting that triamcinolone hexacetonide is more efficient that triamcinolone acetonide inducing local remission.

Recently, Hinze et al. have developed practice- and consensus-based strategies regarding the diagnosis and treatment of systemic JIA in Germany [34]. In these strategies, high dose systemic glucocorticoids are regarded as an effective and proven treatment for systemic JIA. High-dose glucocorticoids either in IV pulse or daily oral therapy are recommended as an initial option in systemic JIA treatment which could be repeated in case of inefficient treatment response. Systemic glucocorticoids may also be used as a complimentary therapy during the initial treatment. IAGI can be used at any time for treatment of arthritis in systemic JIA.

Adverse events

Glucocorticoid administration is associated with many adverse events (Table 2). Both the average dose and cumulative duration of glucocorticoid use affect the occurrence of adverse events; however, established thresholds for the dose and duration of glucocorticoid treatment are not available [35].

The main disadvantage of glucocorticoids is the toxic and metabolic adverse events associated with long-term systemic use at supraphysiological doses [36]. Adrenal insufficiency, growth restriction, Cushing's syndrome, weight gain, atherosclerosis, hypertension, hyperlipidemia, hyperglycemia or corticosteroid-induced diabetes, osteoporosis, osteonecrosis, cataract, glaucoma, gastritis, myopathy, steatohepatitis, skin pathologies (striae, skin atrophy, acne, impaired wound healing, etc.), psychosis, mood disorders, and increased risk for infections could be seen with glucocorticoid use [10, 37, 38]. Some of these adverse events which are more critical for children with JIA have been discussed in detail below.

Growth restriction

Glucocorticoid treatment interferes with growth through several mechanisms including inhibiting bone formation, promoting bone resorption, and decreasing growth hormone secretion [39].

Recently, McErlane et al. reported growth restriction over 3 years after diagnosis in 39% of JIA patients [40]. The greatest decrease in height *Z* score was in systemic JIA patients 90% of whom used systemic glucocorticoids

Table 2 The main adverse events associated with glucocorticoid treatment

Type of glucocorticoid treatment	Adverse events
Systemic use	Adrenal suppression/insufficiency
	Growth restriction
	Cushing's syndrome
	Weight gain
	Atherosclerosis
	Hypertension
	Hyperlipidemia
	Hyperglycemia/diabetes
	Osteoporosis
	Osteonecrosis
	Cataract
	Glaucoma
	Myopathy
	Gastritis
	Steatohepatitis
	Skin pathologies (striae, skin atrophy, acne, impaired wound healing, etc.)
	Psychosis
	Mood disorders
	Increase risk for infections
Intraarticular injection	Local atrophy (cutaneous/subcutaneous)
	Local hypopigmentation
	Injection-related adverse events (e.g. Nicolau syndrome)
	Adverse events associated with systemic use (rare)
Ocular topical use	Cataract
	Glaucoma
	Adverse events associated with systemic use (rare)

for a median of 46.6 weeks. It seems likely that both systemic glucocorticoid use and chronic inflammation from the disease itself contributed to the growth restriction in these patients [40]. Klotsche et al. investigated the outcome and treatment regimens in 597 systemic JIA patients from 2000 to 2013 [7]. They found that treatment with systemic glucocorticoids and DMARDs remained stable over the period. Growth restriction was associated both with high disease activity and use of systemic glucocorticoids. It is important to note that one-third of the patients were still on systemic glucocorticoids at the 3-year follow-up [7]. Guzman et al. reported that new onset short stature was more frequent among patients with systemic JIA than those with other JIA subcategories [8]. Both higher systemic glucocorticoid use and/or more intense chronic inflammation in systemic JIA could be contributing to this result.

Growth hormone is used in the treatment of glucocorticoid-induced growth restriction [41–43]. Adverse events associated with growth hormone include disease reactivation [41]. This may be through induction of proinflammatory cytokines by growth hormone; however, the exact mechanism remains unknown [44]. Thus, growth hormone should be used cautiously in JIA with close follow-up of disease activity.

Adrenal suppression

As a result of exposure of the hypothalamic–pituitary–adrenal (HPA) axis to exogenous corticosteroids, adrenal suppression may occur which leads to decreased cortisol production [45]. Timing, dose, and duration of glucocorticoid therapy could affect the development of adrenal suppression [46]. Abrupt cessation of long-term glucocorticoid therapy without adequate tapering or occurrence of stressful conditions such as surgery or severe infection while the patient is on glucocorticoid therapy could cause adrenal insufficiency due to adrenal suppression. Ahmet et al. reported that more than half of their pediatric patients with rheumatic disease (JIA being the most common diagnosis) experienced adrenal suppression after glucocorticoid discontinuation despite a gradual tapering [45]. The median duration of adrenal suppression was 7 months in this study. They suggested that stress dosing should be considered in patients even after discontinuation of glucocorticoids.

Adrenal suppression should be considered in all children receiving glucocorticoids at supraphysiological doses (> 8–12 mg/m^2/day hydrocortisone or equivalent) for > 2 weeks [47]. It is important to keep in mind that even low doses of therapeutic glucocorticoids could cause adrenal suppression. In addition, multiple short-course high-dose glucocorticoid therapy could cause adrenal suppression especially if the total exceeds 3 weeks in the last 6 months [48].

Adrenal suppression could be overlooked until adrenal crisis occurs in case of a physiological stress such as illness or surgery. To avoid adrenal crisis, adequate and careful tapering before glucocorticoid cessation and adjusting glucocorticoid doses in case of a physical stress are important [47]. Morning doses, lower doses, and shorter duration lower the risk of adrenal suppression [45, 46, 49]. Tapering is critical; however, we lack evidence-based guidelines for glucocorticoid tapering.

The initial screening test for adrenal suppression is testing morning cortisol levels which could be followed by low-dose adrenocorticotropic hormone stimulation test [47, 50]. It is important to note that adrenal suppression risk is higher in children with Cushing's syndrome [51].

Osteoporosis

Inflammation, glucocorticoid therapy, and immobilization all contribute to the suppression of the bone mass in JIA [52]. Thus, JIA itself is associated with reduced bone mineral density (BMD) independent of glucocorticoid exposure [53, 54].

Vertebral fractures are considered as important manifestations of osteoporosis. Le Blanc et al. observed 29 incident vertebral fractures in 14 out of 134 children with rheumatic diseases (50 with JIA) during the 3 years following glucocorticoid initiation [55]. Every 0.5 mg/kg increase in average daily glucocorticoid dose (prednisone equivalent) was associated with a two-fold increase in fracture risk. Besides glucocorticoid treatment, increase in disease severity scores, increase in body mass index, and decrease in lumbar spine BMD were associated with increased risk for vertebra fractures [55]. Rodd et al. demonstrated that 6% of children with glucocorticoid-treated rheumatic diseases had incident vertebral fractures 12 months after glucocorticoid initiation [56]. In their study, 36.7% of children had JIA and half of these patients had systemic JIA [56].

There is no specific definition for glucocorticoid-induced osteoporosis in children. Definitions for osteoporosis in pediatrics could be used for diagnosis. According to the 2013 PDC (the Pediatric Position Developmental Conference) revised criteria, the finding of one or more vertebral compression fractures in the absence of local disease or high energy trauma is definitive for osteoporosis in children [57]. In the absence of vertebral compression fractures, the combination of both a clinically significant fracture history and a reduced bone mass for age and sex (*Z* score of BMD below −2 at the spine L1-4 and/or total body less head) is required for diagnosis of osteoporosis [57]. Clinically significant fracture history is regarded as the presence of ≥ 2 long-bone fractures by the age 10 years or ≥ 3 long-bone fractures by the age 19 years. The PDC strongly recommends the use of dual X-ray absorptiometry (DXA) for evaluating BMD [57]. Of note, sitting height could be used as a surrogate for the length of spinal column and could provide clue about the presence of silent vertebral compression fractures [58].

Osteonecrosis

Osteonecrosis (also known as aseptic/avascular/ischemic necrosis or bone infarct) is the result of a reduction/loss of blood supply to bone [59, 60]. Systemic glucocorticoid use is the leading cause of non-traumatic osteonecrosis [61]. It is most commonly observed after long-term high dose glucocorticoid use [61]; however, it may occur after short-term exposure to glucocorticoids or by IAGI [62]. Osteonecrosis is mainly the disease of adults in the 4th–5th decades of life [59] and it has not been commonly reported in JIA patients. Since skeletal remodeling and plasticity is high in children, children could be less prone to glucocorticoid-induced osteonecrosis than adults [63, 64]. The studies about the association of osteonecrosis and glucocorticoid use in children are mainly focused on patients with hematologic malignancies and there are scarce data about osteonecrosis in glucocorticoid-using JIA patients. In a population-based cohort study investigating the association of oral glucocorticoid use and osteonecrosis in children and adults with chronic inflammatory diseases, the authors observed that glucocorticoid use was clearly associated with osteonecrosis in a dose-related fashion in adults while this risk was not detectable in children [63]. It is important to note that autoimmune arthritis itself was independently associated with osteonecrosis [63].

In case of osteonecrosis, pain and reduction in range of motion could be observed; however, the patients could also be asymptomatic. The features in imaging are important for diagnosis and include rim of sclerosis on plain radiographs, photopenia in early disease at bone scintigraphy, and maintained yellow marrow at magnetic resonance imaging with a serpentine rim of high signal intensity (double-line sign) [60]. It is important to diagnose osteonecrosis early before the damage becomes irreversible [35]. Both non-invasive and invasive therapeutic options exist for osteonecrosis. Non-invasive measures include reduction of mechanical stress, physical therapy, extracorporeal shock wave treatment, hyperbaric oxygen treatment, and pharmacologic agents such as vasodilators [60]. Surgical treatment could

be used for both prophylaxis (for preventing the progression of articular collapse) and reconstruction [60].

Ocular adverse events

The major ophthalmologic adverse events of glucocorticoids are cataract and glaucoma. In a study including 75 children with JIA-associated uveitis, Thorne et al. reported that almost half of these patients experienced cataract at any point in follow-up [65]. The presence of posterior synechiae, active uveitis, and topical glucocorticoid use were significantly associated with cataract development and use of topical glucocorticoids was associated with cataract formation independent of uveitis activity. Of note, compared to eyes treated with topical glucocorticoids > 3 drops/day, treatment with ≤ 3 drops/day of topical glucocorticoids and concomitant use of other forms of glucocorticoids were associated with a lower risk of cataract. Stroh et al. have recently demonstrated that 40% of 196 examined eyes of 108 patients with JIA-associated uveitis had ocular hypertension or secondary glaucoma [66]. Presenting with anterior uveitis, active inflammation, and systemic glucocorticoid use were risk factors for developing ocular hypertension [66].

Both the dose and duration of glucocorticoid therapy seem to affect the risk for ocular adverse events. However, even small doses of glucocorticoids could lead to development of these side effects [67]. It is important to note that active ocular inflammation is also a risk factor for cataract, ocular hypertension and secondary glaucoma besides systemic/topical glucocorticoid use [68]. Especially if the child has growth suppression associated with glucocorticoids, risk for cataracts increases [69]. Ophthalmologic examination could be performed at baseline and after the initiation of glucocorticoids.

Infections

Since glucocorticoids affect both adaptive and innate immune system, the risk for bacterial, viral, and fungal infections may increase with glucocorticoid use [70–73]. There is no safe lower dose threshold for glucocorticoids for infection risk at therapeutic doses. For increased risk of tuberculosis, the Center of Disease Control and Prevention (CDC) and the American Thoracic Society define the threshold as prednisone 15 mg or equivalent daily for > 1 month [74]. The EULAR Task Force has highlighted important points about long-term systemic glucocorticoid therapy and infection risk [19]. According to these viewpoints, the current glucocorticoid dose is more risk-relevant than former usage or cumulative dose. And the level of harm of glucocorticoids depends on patient-specific risk factors (comorbidities, infection exposure, etc.) besides glucocorticoid dose [19].

Giving the lowest dose with the quickest taper and shortest duration possible for control of the disease is very important to decrease the aforementioned adverse events of glucocorticoids. Besides, preferring alternate day dosing or intermittent IV pulses over daily oral use and early introduction of glucocorticoid-sparing agents could lower the risk for adverse events [36, 75].

Vaccination of JIA patients who are on systemic glucocorticoid treatment

For vaccination of JIA patients who are on systemic glucocorticoids, two points are critical to consider: (1) to prevent occurrence of infection with vaccine and (2) to get a protective vaccine response.

In 2011, EULAR recommendations were published for vaccination in pediatric patients with rheumatic diseases [16]. According to these recommendations, non-live vaccines could be administered to patients on glucocorticoid therapy, when indicated. However, pathogen-specific antibody concentrations should be checked after vaccination in patients on high dose glucocorticoids (≥ 2 mg/kg or a total dose of ≥ 20 mg/day for ≥ 2 weeks). It is recommended to withhold live-attenuated vaccines in patients who are on high dose glucocorticoids [16].

Although patients on systemic glucocorticoids present lower seroconversion rates, they usually reach protective antibody titers [76]. In a recent systematic literature review on vaccination in pediatric patients with systemic inflammatory rheumatic diseases, glucocorticoids did not seem to significantly hamper the immune response to vaccines [77].

There is no evidence-based data to determine the "safe" time for glucocorticoid initiation after live vaccines; however, it is considered as minimum of 2–4 weeks for clearance of live virus [71].

General measures for JIA patients who are/will be on systemic glucocorticoid therapy

It is recommended to discuss/consider adverse events of glucocorticoid therapy with the patient/parents before initiating treatment (Table 3). A card stating the date of initiation of glucocorticoids, the dose and tapering regimen could be provided if the therapy will be prolonged [78]. About follow-up, monitoring body weight, linear growth, bone health, blood pressure, peripheral oedema, cardiac insufficiency, serum lipids, blood and/or urine glucose, and glaucoma/cataract is advisable [78]. At baseline, an elaborative examination of nutritional, pubertal, growth, and vaccination status and measurement of body weight and height, blood pressure, BMD, complete blood count,

Table 3 General measures for following juvenile idiopathic arthritis patients on systemic glucocorticoid therapy

1. Discussing adverse events with patients/parents before initiation of treatment
2. Evaluating concomitant therapies for drug–drug interactions and adverse events
3. Providing an information card for the patient including dose, initiation date, and tapering regimen (especially for long-term therapy)
4. Evaluating growth (body weight and height) and pubertal status at baseline and during follow-up
5. Evaluating the nutritional status of the patient and arranging diet (low sodium, low glucose, low calories, high protein)
6. Evaluating bone health at baseline and during follow-up (with annual bone mineral density measurement)
7. Encouraging participation in regular physical activity
8. Calcium and vitamin D supplementation
9. Measuring blood pressure and basic laboratory tests (complete blood count, blood/urine glucose, lipid profile) at baseline and during follow-up
10. Baseline and follow-up ophthalmologic examination (for cataract and glaucoma)
11. Planning for vaccination
12. Planning for dose adjustments in stressful conditions (surgery, infection, etc.)

blood glucose, lipid profile should be performed if prolonged systemic glucocorticoid treatment is planned [10]. Concomitant therapies such as NSAIDs are important to consider certain precautions such as initiating proton pump inhibitors for gastro-protection. Drug–drug interactions should also be considered since glucocorticoids modify CYP450 enzyme system activity like many other drugs [79].

Bone health monitoring includes evaluation of calcium and vitamin D intake, physical activity, back pain, and disease-related risk factors for bone loss such as chronic inflammation [10]. Annual BMD measurement for screening osteoporosis should be performed in the follow-up of JIA patients on long-term glucocorticoid therapy [36]. According to the 2017 ACR guideline for the prevention and treatment of glucocorticoid-induced osteoporosis, children should be evaluated for clinical fracture risk within 6 months of the start of glucocorticoid therapy with re-evaluation every 12 months [80]. In children (4–17 years of age) treated with glucocorticoids for ≥ 3 months, it is recommended to optimize calcium intake (1000 mg/day) and vitamin D intake (600 IU/day) and lifestyle modifications (balanced diet, regular exercise, etc.) [80]. In children (4–17 years of age) with an osteoporotic fracture who are continuing treatment with glucocorticoids at a dose of ≥ 0.1 mg/kg/day for ≥ 3 months, treatment with an oral bisphosphonate (intravenous if oral treatment is contraindicated) plus calcium and vitamin D is recommended [80]. However, these treatment recommendations are noted as conditional recommendations because of very low-quality anti-fracture data in children. Although bisphosphonates are recommended both for prevention and treatment of glucocorticoid-induced osteoporosis in adults [80]; the appropriate use is not certain in children. Recently, Inoue et al. have shown that the early use of bisphosphonates might have a bone-protective effect in glucocorticoid-treated children with rheumatic diseases [81]. With regards to bisphosphonates, one should keep in mind the potential severe consequences such as growth impairment (unproven) and teratogenicity [82].

Participation in regular physical activity and healthy low-calorie diet are important to prevent glucocorticoid-induced weight gain, diabetes, and hyperlipidemia. However, there are scarce data about dietetic measures in case of glucocorticoid therapy. Sufficient potassium intake, low sodium and little glucose intake, high protein intake, and low calories are the main features of the dietary recommendations for patients on systemic glucocorticoids [83]. However, there are no controlled studies to determine the threshold dose and duration of systemic glucocorticoid therapy for dietary precautions.

Lastly, glucocorticoid doses should be adjusted in case of additional stressful conditions such as surgery or infections [51].

Intraarticular glucocorticoid injections

Intraarticular glucocorticoid injections remain the first-line treatment especially in oligoarthritis. IAGIs to multiple joints have increased in medical practice currently, as well. In case of polyarticular involvement, IAGI could also be applied to only a small number of recalcitrant joints that do not respond to intensive systemic therapy [84]. The recommendations with regard to IAGI in guidelines have been discussed above.

In the systematic review on the clinical effectiveness of IAGI for lower limb arthritis in JIA, Jennings et al. found weak levels of evidence for IAGIs decreasing tenderness/pain, swelling, synovitis, clinical signs and symptoms, increasing range of motion in lower limb joints, and improving medical imaging disease-related outcomes such as joint effusion, synovial hypertrophy, and erosion [85]. Several factors can modify the effectiveness of IAGI. Previously, it was demonstrated that JIA patients with a higher erythrocyte

sedimentation rate were more likely to benefit from IAGI of the knees [86]. In a study including 220 JIA patients with 1096 IAGI, positive C-reactive protein value, negative antinuclear antibody, lack of concomitant methotrexate administrations, and a polyarticular (versus an oligoarticular) disease course were the strongest predictors for synovitis flare after IAGI [87]. Ravelli et al. have recently demonstrated that concomitant use of methotrexate did not improve the effectiveness of IAGI in oligoarticular JIA in a prospective, randomized, open-label trial [88].

For IAGI preparations, triamcinolone hexacetonide has longer duration of action than other preparations [84, 89, 90]. In a double-blind trial on JIA patients, Zulian et al. showed that triamcinolone hexacetonide was superior to triamcinolone acetonide in IAGI [90]. Although triamcinolone hexacetonide is the optimal glucocorticoid for IAGI, use of more soluble glucocorticoids such as methylprednisolone acetate is advisable for small joints [91]. Doses for triamcinolone hexacetonide range between 0.25 and 1.5 mg/kg depending on child's and joint's size (e.g., 0.25–0.5 mg/kg for wrist; 1–1.5 mg/kg for knee or hip) [84, 91]. And the doses for methylprednisolone acetate range between 5 and 10 mg for small joints such as metacarpophalangeal and interphalangeal joints [91]. There is a lack of standardization and evidence on injection techniques, use of local anesthetics, and post-injection strategies such as immobilization or avoidance of physical activity [85].

Adverse events are seen in around 2% of IAGI [90]. Localized atrophy (cutaneous or subcutaneous) is the most common adverse event [84, 92]. IAGI could cause systemic adverse events such as Cushingoid habitus, transient adrenal suppression, acneiform rashes, and insomnia [84, 93–95]. Injection-related side effects could be observed after IAGI, as well. Even Nicolau syndrome (also known as livedoid dermatitis or embolia cutis medicamentosa) was reported after IAGI [96].

Glucocorticoids in treatment of JIA-associated uveitis

Chronic anterior uveitis develops in 10–15% of children with JIA [97, 98]. Timely diagnosis and appropriate management are critical to prevent vision loss and ocular complications.

CARRA CTPs for JIA-associated chronic anterior uveitis have been published recently [99]. Two CTPs have been defined; one for methotrexate and one for tumor necrosis factor (TNF) inhibitors. Both of these CTPs are suitable for patients with uveitis resistant to topical glucocorticoids. Thus, topical glucocorticoids have been regarded as the primary treatment for JIA-associated uveitis. They mentioned that methotrexate or TNF inhibitor CTPs could also be applied to children on systemic glucocorticoids and with a history of unsuccessful subtenar steroid injections. There is no CTP including systemic glucocorticoids since this treatment is usually managed by ophthalmologists rather than rheumatologists. However, expert opinion is to avoid systemic glucocorticoids in chronic anterior uveitis treatment. It could be started as a bridging therapy while waiting for glucocorticoid-sparing agents to be effective. It is important to note that systemic glucocorticoids should be tapered in 2 weeks after the initiation of glucocorticoid-sparing agents.

Systemic glucocorticoids were addressed in a clinical management algorithm for JIA-associated uveitis based on interdisciplinary panel (including ophthalmologists and pediatric rheumatologists) consensus reported in 2015 [100]. According to this algorithm, oral prednisolone (or equivalent) at doses of 1–2 mg/kg/day could be initiated in JIA patients with grade 3 + and 4 + uveitis without improvement with topical glucocorticoids. The dose could be reduced when improvement is observed as the effect of a biologic or non-biologic DMARD manifests [100].

The SHARE (Single Hub and Access point for pediatric Rheumatology in Europe) initiative has also provided recommendations for the diagnosis and treatment of JIA-associated uveitis; mainly chronic anterior uveitis, recently [101]. In SHARE recommendations, topical glucocorticoids (preferably prednisolone acetate or dexamethasone) are designated as the first-line treatment of anterior uveitis. There is no reference to systemic glucocorticoids as a treatment option in JIA-associated uveitis. However, in the text, the authors mentioned that systemic glucocorticoids may be helpful for rapid control of severe uveitis or in the presence of macular oedema. When there is need for systemic immunosuppression, methotrexate is the first choice. And in case of methotrexate inefficacy/intolerance, initiating biologic drugs are recommended.

The main adverse events related with topical ocular glucocorticoids are cataract formation and glaucoma as mentioned above [101]. It is important to switch to systemic treatment when risks associated with high doses of topical glucocorticoids outweigh the beneficial effects.

Local ocular injectable therapy with glucocorticoid implants remains as an option especially in patients with severe persistent ocular inflammation or macular oedema [102, 103].

Glucocorticoids in macrophage activation syndrome (MAS) treatment

Macrophage activation syndrome is a form of reactive hemophagocytic lymphohistiocytosis occurring in 6–8% of systemic JIA patients and it is a life-threatening medical emergency [104].

High dose glucocorticoid therapy is regarded as the first-line treatment in systemic JIA-associated MAS [105]. Other therapeutic options include cyclosporine A, intravenous immunoglobulin (IVIG), etoposide, and cytokine-targeting biologic drugs.

High dose glucocorticoids are usually administered in the form of IV pulse methylprednisolone therapy [105, 106]. However, Nakagishi et al. reported that dexamethasone palmitate, a liposome-incorporated dexamethasone, inhibited inflammation effectively in four MAS patients (JIA-associated MAS in three of them) who did not respond to pulse methylprednisolone therapy sufficiently [107].

In a large series including 362 children with systemic JIA-associated MAS, almost all patients received systemic glucocorticoids mostly in IV form [108]. Of note, two-thirds of patients received cyclosporine A, one-third IVIG, and 15% received biologic drugs with anakinra being the most prevalent choice.

Conclusion

We have been using glucocorticoids effectively in JIA treatment for almost 60 years. There are many adverse events associated with glucocorticoids most of which could be prevented with the optimum use of this therapy. However, the benefits and risks of glucocorticoid therapy should be continuously balanced throughout the treatment. And the dose/duration of treatment should be tailored according to each patient instead of applying general recommendations which are mainly based on observational or retrospective studies and expert opinion. Data from the literature guide us to use glucocorticoids in an optimum way in JIA enlightening the issues especially about the indications of IAGI and systemic use in systemic JIA and MAS. However, there is still lack of evidence and need for prospective randomized studies in most parts including the indications in different subcategories of JIA, the optimum dose/route of administration/duration of treatment, and tapering strategies.

Author contributions EDB designed the structure of the article, drafted and critically revised the text, and approved the final version of the manuscript.

Funding No funding was received for this study.

Compliance with ethical standards

Conflict of interest Ezgi Deniz Batu declares that she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by the author.

References

1. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, Suarez-Almazor ME, Woo P, International League of Associations for R (2004) International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton 2001. J Rheumatol 31:390–392
2. Blazina S, Markelj G, Avramovic MZ, Toplak N, Avcin T (2016) Management of juvenile idiopathic arthritis: a clinical guide. Paediatr Drugs 18:397–412. https://doi.org/10.1007/s40272-016-0186-0
3. Beukelman T, Ringold S, Davis TE, DeWitt EM, Pelajo CF, Weiss PF, Kimura Y, Investigators CR (2012) Disease-modifying antirheumatic drug use in the treatment of juvenile idiopathic arthritis: a cross-sectional analysis of the CARRA Registry. J Rheumatol 39:1867–1874. https://doi.org/10.3899/jrheum.120110
4. Stoll ML, Cron RQ (2014) Treatment of juvenile idiopathic arthritis: a revolution in care. Pediatr Rheumatol Online J 12:13. https://doi.org/10.1186/1546-0096-12-13
5. Beukelman T, Kimura Y, Ilowite NT, Mieszkalski K, Natter MD, Burrell G, Best B, Jones J, Schanberg LE, Investigators CR (2017) The new Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry: design, rationale, and characteristics of patients enrolled in the first 12 months. Pediatr Rheumatol Online J 15:30. https://doi.org/10.1186/s12969-017-0160-6
6. Guzman J, Oen K, Tucker LB, Huber AM, Shiff N, Boire G, Scuccimarri R, Berard R, Tse SM, Morishita K, Stringer E, Johnson N, Levy DM, Duffy KW, Cabral DA, Rosenberg AM, Larche M, Dancey P, Petty RE, Laxer RM, Silverman E, Miettunen P, Chetaille AL, Haddad E, Houghton K, Spiegel L, Turvey SE, Schmeling H, Lang B, Ellsworth J, Ramsey S, Bruns A, Campillo S, Benseler S, Chedeville G, Schneider R, Yeung R, Duffy CM, Re A-Oi (2015) The outcomes of juvenile idiopathic arthritis in children managed with contemporary treatments: results from the ReACCh-Out cohort. Ann Rheum Dis 74:1854–1860. https://doi.org/10.1136/annrheumdis-2014-205372
7. Klotsche J, Raab A, Niewerth M, Sengler C, Ganser G, Kallinich T, Niehues T, Hufnagel M, Thon A, Hospach T, Horneff G, Minden K (2016) Outcome and trends in treatment of systemic juvenile idiopathic arthritis in the German National Pediatric Rheumatologic Database, 2000–2013. Arthritis Rheumatol 68:3023–3034. https://doi.org/10.1002/art.39796
8. Guzman J, Kerr T, Ward LM, Ma J, Oen K, Rosenberg AM, Feldman BM, Boire G, Houghton K, Dancey P, Scuccimarri R, Bruns A, Huber AM, Watanabe Duffy K, Shiff NJ, Berard RA, Levy DM, Stringer E, Morishita K, Johnson N, Cabral DA, Larche M, Petty RE, Laxer RM, Silverman E, Miettunen P, Chetaille AL, Haddad E, Spiegel L, Turvey SE, Schmeling H, Lang B, Ellsworth J, Ramsey SE, Roth J, Campillo S, Benseler S, Chedeville G, Schneider R, Tse SML, Bolaria R, Gross K, Feldman D, Cameron B, Jurencak R, Dorval J, LeBlanc C, St Cyr C, Gibbon M, Yeung RSM, Duffy CM, Tucker LB (2017) Growth and weight gain in children with juvenile idiopathic arthritis: results from the ReACCh-Out cohort. Pediatr Rheumatol Online J 15:68. https://doi.org/10.1186/s12969-017-0196-7
9. Gasparyan AY, Ayvazyan L, Blackmore H, Kitas GD (2011) Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. Rheumatol Int 31:1409–1417. https://doi.org/10.1007/s00296-011-1999-3
10. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, Brown JP, Cohen A, Kim H (2013) A practical guide

to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol 9:30. https://doi.org/10.1186/1710-1492-9-30
11. Cruz-Topete D, Cidlowski JA (2015) One hormone, two actions: anti- and pro-inflammatory effects of glucocorticoids. Neuroimmunomodulation 22:20–32. https://doi.org/10.1159/000362724
12. Uhlenhaut NH, Barish GD, Yu RT, Downes M, Karunasiri M, Liddle C, Schwalie P, Hubner N, Evans RM (2013) Insights into negative regulation by the glucocorticoid receptor from genome-wide profiling of inflammatory cistromes. Mol Cell 49:158–171. https://doi.org/10.1016/j.molcel.2012.10.013
13. Stahn C, Buttgereit F (2008) Genomic and nongenomic effects of glucocorticoids. Nat Clin Pract Rheumatol 4:525–533. https://doi.org/10.1038/ncprheum0898
14. Ayroldi E, Cannarile L, Migliorati G, Nocentini G, Delfino DV, Riccardi C (2012) Mechanisms of the anti-inflammatory effects of glucocorticoids: genomic and nongenomic interference with MAPK signaling pathways. FASEB J 26:4805–4820. https://doi.org/10.1096/fj.12-216382
15. Buttgereit F, da Silva JA, Boers M, Burmester GR, Cutolo M, Jacobs J, Kirwan J, Kohler L, Van Riel P, Vischer T, Bijlsma JW (2002) Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. Ann Rheum Dis 61:718–722
16. Heijstek MW, Ott de Bruin LM, Bijl M, Borrow R, van der Klis F, Kone-Paut I, Fasth A, Minden K, Ravelli A, Abinun M, Pileggi GS, Borte M, Wulffraat NM, Eular (2011) EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. Ann Rheum Dis 70:1704–1712. https://doi.org/10.1136/ard.2011.150193
17. Schimmer BPPK (2001) Adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In: Hardman JG, Limbird LE, Gilman AG (eds) Goodman and Gilman's the pharmacological basis of therapeutics. McGraw-Hill, Medical Pub. Division, New York, pp 1469–1679
18. Panoulas VF, Douglas KM, Stavropoulos-Kalinoglou A, Metsios GS, Nightingale P, Kita MD, Elisaf MS, Kitas GD (2008) Long-term exposure to medium-dose glucocorticoid therapy associates with hypertension in patients with rheumatoid arthritis. Rheumatology 47:72–75. https://doi.org/10.1093/rheumatology/kem311
19. Strehl C, Bijlsma JW, de Wit M, Boers M, Caeyers N, Cutolo M, Dasgupta B, Dixon WG, Geenen R, Huizinga TW, Kent A, de Thurah AL, Listing J, Mariette X, Ray DW, Scherer HU, Seror R, Spies CM, Tarp S, Wiek D, Winthrop KL, Buttgereit F (2016) Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force. Ann Rheum Dis 75:952–957. https://doi.org/10.1136/annrheumdis-2015-208916
20. Malattia C, Martini A (2014) Glucocorticoids in juvenile idiopathic arthritis. Ann N Y Acad Sci 1318:65–70. https://doi.org/10.1111/nyas.12436
21. Schiappapietra B, Varnier G, Rosina S, Consolaro A, Martini A, Ravelli A (2015) Glucocorticoids in juvenile idiopathic arthritis. Neuroimmunomodulation 22:112–118. https://doi.org/10.1159/000362732
22. Morrow SA, Stoian CA, Dmitrovic J, Chan SC, Metz LM (2004) The bioavailability of IV methylprednisolone and oral prednisone in multiple sclerosis. Neurology 63:1079–1080
23. Ilowite NT, Sandborg CI, Feldman BM, Grom A, Schanberg LE, Giannini EH, Wallace CA, Schneider R, Kenney K, Gottlieb B, Hashkes PJ, Imundo L, Kimura Y, Lang B, Miller M, Milojevic D, O'Neil KM, Punaro M, Ruth N, Singer NG, Vehe RK, Verbsky J, Woodward A, Zemel L (2012) Algorithm development for corticosteroid management in systemic juvenile idiopathic arthritis trial using consensus methodology. Pediatr Rheumatol Online J 10:31. https://doi.org/10.1186/1546-0096-10-31
24. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, Ilowite NT, Kimura Y, Laxer RM, Lovell DJ, Martini A, Rabinovich CE, Ruperto N (2011) 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res 63:465–482. https://doi.org/10.1002/acr.20460
25. Huppertz HI (2011) Recommendations for juvenile idiopathic arthritis by the American College of Rheumatology: comment on the article by Beukelman et al. Arthritis Care Res 63:1354–1355. https://doi.org/10.1002/acr.20521 author reply 1355–1356.
26. Ringold S, Weiss PF, Beukelman T, Dewitt EM, Ilowite NT, Kimura Y, Laxer RM, Lovell DJ, Nigrovic PA, Robinson AB, Vehe RK, American College of R (2013) 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Care Res 65:1551–1563. https://doi.org/10.1002/acr.22087
27. Cellucci T, Guzman J, Petty RE, Batthish M, Benseler SM, Ellsworth JE, Houghton KM, Le BC, Huber AM, Luca N, Schmeling H, Shiff NJ, Soon GS, Tse SM, Pediatric Committee of the Canadian Rheumatology A (2016) Management of juvenile idiopathic arthritis 2015: a position statement from the Pediatric Committee of the Canadian Rheumatology Association. J Rheumatol 43:1773–1776. https://doi.org/10.3899/jrheum.160074
28. DeWitt EM, Kimura Y, Beukelman T, Nigrovic PA, Onel K, Prahalad S, Schneider R, Stoll ML, Angeles-Han S, Milojevic D, Schikler KN, Vehe RK, Weiss JE, Weiss P, Ilowite NT, Wallace CA,, Research A (2012) Juvenile Idiopathic Arthritis Disease-specific Research Committee of Childhood Arthritis R. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. Arthritis Care Res 64:1001–1010. https://doi.org/10.1002/acr.21625
29. Kimura Y, DeWitt EM, Beukelman T, Stoll ML, Nigrovic PA, Onel K, Prahalad S, Angeles-Han S, Schneider R, Juvenile Idiopathic Arthritis Disease-Specific Research Committee of the Childhood A, Rheumatology Research A (2014) Adding canakinumab to the Childhood Arthritis and Rheumatology Research Alliance consensus treatment plans for systemic juvenile idiopathic arthritis: comment on the article by DeWitt et al. Arthritis Care Res 66:1430–1431. https://doi.org/10.1002/acr.22343
30. Ringold S, Weiss PF, Colbert RA, DeWitt EM, Lee T, Onel K, Prahalad S, Schneider R, Shenoi S, Vehe RK, Kimura Y, Juvenile Idiopathic Arthritis Research Committee of the Childhood A, Rheumatology Research A (2014) Childhood Arthritis and Rheumatology Research Alliance consensus treatment plans for new-onset polyarticular juvenile idiopathic arthritis. Arthritis Care Res 66:1063–1072. https://doi.org/10.1002/acr.22259
31. Kimura Y, Grevich S, Beukelman T, Morgan E, Nigrovic PA, Mieszkalski K, Graham TB, Ibarra M, Ilowite N, Klein-Gitelman M, Onel K, Prahalad S, Punaro M, Ringold S, Toib D, Van Mater H, Weiss JE, Weiss PF, Schanberg LE, Investigators CR (2017) Pilot study comparing the childhood arthritis & rheumatology research alliance (CARRA) systemic juvenile idiopathic arthritis consensus treatment plans. Pediatr Rheumatol Online J 15:23. https://doi.org/10.1186/s12969-017-0157-1
32. Nigrovic PA, Beukelman T, Tomlinson G, Feldman BM, Schanberg LE, Kimura Y, Childhood A, Rheumatology Research Alliance Systemic Juvenile Idiopathic Arthritis Consensus Treatment Plan W (2018) Bayesian comparative effectiveness study of four consensus treatment plans for initial management of systemic

juvenile idiopathic arthritis: FiRst-Line options for systemic juvenile idiopathic arthritis treatment (FROST). Clin Trials 15:268–277. https://doi.org/10.1177/1740774518761367
33. Dueckers G, Guellac N, Arbogast M, Dannecker G, Foeldvari I, Frosch M, Ganser G, Heiligenhaus A, Horneff G, Illhardt A, Kopp I, Krauspe R, Markus B, Michels H, Schneider M, Singendonk W, Sitter H, Spamer M, Wagner N, Niehues T (2012) Evidence and consensus based GKJR guidelines for the treatment of juvenile idiopathic arthritis. Clin Immunol 142:176–193. https://doi.org/10.1016/j.clim.2011.10.003
34. Hinze CH, Holzinger D, Lainka E, Haas JP, Speth F, Kallinich T, Rieber N, Hufnagel M, Jansson AF, Hedrich C, Winowski H, Berger T, Foeldvari I, Ganser G, Hospach A, Huppertz HI, Monkemoller K, Neudorf U, Weissbarth-Riedel E, Wittkowski H, Horneff G, Foell D, Collaborators P-KSp (2018) Practice and consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis in Germany. Pediatr Rheumatol Online J 16:7. https://doi.org/10.1186/s12969-018-0224-2
35. Caplan A, Fett N, Rosenbach M, Werth VP, Micheletti RG (2017) Prevention and management of glucocorticoid-induced side effects: a comprehensive review: a review of glucocorticoid pharmacology and bone health. J Am Acad Dermatol 76:1–9. https://doi.org/10.1016/j.jaad.2016.01.062
36. Higgins GC (2018) Complications of treatments for pediatric rheumatic diseases. Pediatr Clin N Am 65:827–854. https://doi.org/10.1016/j.pcl.2018.04.008
37. Aljebab F, Choonara I, Conroy S (2017) Systematic review of the toxicity of long-course oral corticosteroids in children. PloS One 12:e0170259. https://doi.org/10.1371/journal.pone.0170259
38. Amann J, Wessels AM, Breitenfeldt F, Huscher D, Bijlsma JWJ, Jacobs JWG, Buttgereit F (2017) Quantifying cutaneous adverse effects of systemic glucocorticoids in patients with rheumatoid arthritis: a cross-sectional cohort study. Clin Exp Rheumatol 35:471–476
39. Caplan A, Fett N, Rosenbach M, Werth VP, Micheletti RG (2017) Prevention and management of glucocorticoid-induced side effects: a comprehensive review: ocular, cardiovascular, muscular, and psychiatric side effects and issues unique to pediatric patients. J Am Acad Dermatol 76:201–207. https://doi.org/10.1016/j.jaad.2016.02.1241
40. McErlane F, Carrasco R, Kearsley-Fleet L, Baildam EM, Wedderburn LR, Foster HE, Ioannou Y, Chieng SEA, Davidson JE, Thomson W, Hyrich KL (2018) Growth patterns in early juvenile idiopathic arthritis: results from the Childhood Arthritis Prospective Study (CAPS). Semin Arthritis Rheum 48:53–60. https://doi.org/10.1016/j.semarthrit.2017.11.002
41. Frittoli RB, Longhi BS, Silva AM, Filho AAB, Monteiro M, Appenzeller S (2017) Effects of the use of growth hormone in children and adolescents with juvenile idiopathic arthritis: a systematic review. Rev Bras Reumatol Engl Ed 57:100–106. https://doi.org/10.1016/j.rbre.2016.07.009
42. Kim JY, Kim HS, Park SH (2015) Disease flare after 7 year-remission of systemic type juvenile idiopathic arthritis: is growth hormone therapy a culprit or innocent bystander? Int J Rheum Dis 18:377–378. https://doi.org/10.1111/1756-185X.12385
43. Simon D, Prieur AM, Quartier P, Charles Ruiz J, Czernichow P (2007) Early recombinant human growth hormone treatment in glucocorticoid-treated children with juvenile idiopathic arthritis: a 3-year randomized study. J Clin Endocrinol Metab 92:2567–2573. https://doi.org/10.1210/jc.2006-2877
44. Bozzola M, De Benedetti F, De Amici M, Jouret B, Travaglino P, Pagani S, Conte F, Tauber M (2003) Stimulating effect of growth hormone on cytokine release in children. Eur J Endocrinol 149:397–401
45. Ahmet A, Brienza V, Tran A, Lemieux J, Aglipay M, Barrowman N, Duffy C, Roth J, Jurencak R (2017) Frequency and duration of adrenal suppression following glucocorticoid therapy in children with rheumatic diseases. Arthritis Care Res (Hoboken) 69:1224–1230. https://doi.org/10.1002/acr.23123
46. Rao RT, Scherholz ML, Androulakis IP (2018) Modeling the influence of chronopharmacological administration of synthetic glucocorticoids on the hypothalamic-pituitary-adrenal axis. Chronobiol Int. https://doi.org/10.1080/07420528.2018.1498098
47. Shulman DI, Palmert MR, Kemp SF, Lawson Wilkins D, Therapeutics C (2007) Adrenal insufficiency: still a cause of morbidity and death in childhood. Pediatrics 119:e484–e494. https://doi.org/10.1542/peds.2006-1612
48. Ahmet A, Kim H, Spier S (2011) Adrenal suppression: a practical guide to the screening and management of this under-recognized complication of inhaled corticosteroid therapy. Allergy Asthma Clin Immunol 7:13. https://doi.org/10.1186/1710-1492-7-13
49. Fisher LE, Ludwig EA, Wald JA, Sloan RR, Middleton E Jr, Jusko WJ (1992) Pharmacokinetics and pharmacodynamics of methylprednisolone when administered at 8 am versus 4 pm. Clin Pharmacol Ther 51:677–688
50. Maguire AM, Biesheuvel CJ, Ambler GR, Moore B, McLean M, Cowell CT (2008) Evaluation of adrenal function using the human corticotrophin-releasing hormone test, low dose Synacthen test and 9am cortisol level in children and adolescents with central adrenal insufficiency. Clin Endocrinol (Oxf) 68:683–691. https://doi.org/10.1111/j.1365-2265.2007.03100.x
51. Alves C, Robazzi TC, Mendonca M (2008) Withdrawal from glucocorticosteroid therapy: clinical practice recommendations. J Pediatr (Rio J) 84:192–202. https://doi.org/10.2223/JPED.1773 doi
52. Zhang Y, Milojevic D (2017) Protecting bone health in pediatric rheumatic diseases: pharmacological considerations. Paediatr Drugs 19:193–211. https://doi.org/10.1007/s40272-017-0219-3
53. Huber AM, Ward LM (2016) The impact of underlying disease on fracture risk and bone mineral density in children with rheumatic disorders: a review of current literature. Semin Arthritis Rheum 46:49–63. https://doi.org/10.1016/j.semarthrit.2016.02.003
54. Huber AM, Gaboury I, Cabral DA, Lang B, Ni A, Stephure D, Taback S, Dent P, Ellsworth J, LeBlanc C, Saint-Cyr C, Scuccimarri R, Hay J, Lentle B, Matzinger M, Shenouda N, Moher D, Rauch F, Siminoski K, Ward LM, Canadian Steroid-Associated Osteoporosis in the Pediatric Population C (2010) Prevalent vertebral fractures among children initiating glucocorticoid therapy for the treatment of rheumatic disorders. Arthritis Care Res (Hoboken) 62:516–526. https://doi.org/10.1002/acr.20171
55. LeBlanc CM, Ma J, Taljaard M, Roth J, Scuccimarri R, Miettunen P, Lang B, Huber AM, Houghton K, Jaremko JL, Ho J, Shenouda N, Matzinger MA, Lentle B, Stein R, Sbrocchi AM, Oen K, Rodd C, Jurencak R, Cummings EA, Couch R, Cabral DA, Atkinson S, Alos N, Rauch F, Siminoski K, Ward LM, Canadian S-AOiPPC (2015) Incident vertebral fractures and risk factors in the first three years following glucocorticoid initiation among pediatric patients with rheumatic disorders. J Bone Miner Res 30:1667–1675. https://doi.org/10.1002/jbmr.2511
56. Rodd C, Lang B, Ramsay T, Alos N, Huber AM, Cabral DA, Scuccimarri R, Miettunen PM, Roth J, Atkinson SA, Couch R, Cummings EA, Dent PB, Ellsworth J, Hay J, Houghton K, Jurencak R, Larche M, LeBlanc C, Oen K, Saint-Cyr C, Stein R, Stephure D, Taback S, Lentle B, Matzinger M, Shenouda N, Moher D, Rauch F, Siminoski K, Ward LM, Canadian Steroid-Associated Osteoporosis in the Pediatric Population C (2012) Incident vertebral fractures among children with rheumatic disorders 12 months after glucocorticoid initiation: a national observational study. Arthritis Care Res (Hoboken) 64:122–131. https://doi.org/10.1002/acr.20589

57. Gordon CM, Leonard MB, Zemel BS, International Society for Clinical D (2014) 2013 Pediatric Position Development Conference: executive summary and reflections. J Clin Densitom 17:219–224. https://doi.org/10.1016/j.jocd.2014.01.007
58. Chinappen-Horsley U, Blake GM, Fogelman I, Spector TD (2007) A method for determining skeletal lengths from DXA images. BMC Musculoskelet Disord 8:113. https://doi.org/10.1186/1471-2474-8-113
59. Lecouvet FE, Malghem J, Maldague BE, Vande Berg BC (2005) MR imaging of epiphyseal lesions of the knee: current concepts, challenges, and controversies. Radiol Clin N Am 43:655–672, vii-viii. https://doi.org/10.1016/j.rcl.2005.02.002
60. Murphey MD, Foreman KL, Klassen-Fischer MK, Fox MG, Chung EM, Kransdorf MJ (2014) From the radiologic pathology archives imaging of osteonecrosis: radiologic-pathologic correlation. Radiographics 34:1003–1028. https://doi.org/10.1148/rg.344140019
61. Weinstein RS (2012) Glucocorticoid-induced osteoporosis and osteonecrosis. Endocrinol Metab Clin N Am 41:595–611. https://doi.org/10.1016/j.ecl.2012.04.004
62. Nash JJ, Nash AG, Leach ME, Poetker DM (2011) Medical malpractice and corticosteroid use. Otolaryngol Head Neck Surg 144:10–15. https://doi.org/10.1177/0194599810390470
63. Horton DB, Haynes K, Denburg MR, Thacker MM, Rose CD, Putt ME, Leonard MB, Strom BL (2017) Oral glucocorticoid use and osteonecrosis in children and adults with chronic inflammatory diseases: a population-based cohort study. BMJ Open 7:e016788. https://doi.org/10.1136/bmjopen-2017-016788
64. Tsampalieros A, Lam CK, Spencer JC, Thayu M, Shults J, Zemel BS, Herskovitz RM, Baldassano RN, Leonard MB (2013) Long-term inflammation and glucocorticoid therapy impair skeletal modeling during growth in childhood Crohn disease. J Clin Endocrinol Metab 98:3438–3445. https://doi.org/10.1210/jc.2013-1631
65. Thorne JE, Woreta FA, Dunn JP, Jabs DA (2010) Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. Ophthalmology 117:1436–1441. https://doi.org/10.1016/j.ophtha.2009.12.003
66. Stroh IG, Moradi A, Burkholder BM, Hornbeak DM, Leung TG, Thorne JE (2017) Occurrence of and risk factors for ocular hypertension and secondary glaucoma in juvenile idiopathic arthritis-associated uveitis. Ocul Immunol Inflamm 25:503–512. https://doi.org/10.3109/09273948.2016.1142573
67. Caplan A, Fett N, Rosenbach M, Werth VP, Micheletti RG (2017) Prevention and management of glucocorticoid-induced side effects: a comprehensive review: gastrointestinal and endocrinologic side effects. J Am Acad Dermatol 76:11–16. https://doi.org/10.1016/j.jaad.2016.02.1239
68. Angeles-Han S, Yeh S (2012) Prevention and management of cataracts in children with juvenile idiopathic arthritis-associated uveitis. Curr Rheumatol Rep 14:142–149. https://doi.org/10.1007/s11926-011-0229-z
69. Covar RA, Leung DY, McCormick D, Steelman J, Zeitler P, Spahn JD (2000) Risk factors associated with glucocorticoid-induced adverse effects in children with severe asthma. J Allergy Clin Immunol 106:651–659. https://doi.org/10.1067/mai.2000.109830
70. Beukelman T, Xie F, Chen L, Baddley JW, Delzell E, Grijalva CG, Lewis JD, Ouellet-Hellstrom R, Patkar NM, Saag KG, Winthrop KL, Curtis JR, Collaboration S (2012) Rates of hospitalized bacterial infection associated with juvenile idiopathic arthritis and its treatment. Arthritis Rheum 64:2773–2780. https://doi.org/10.1002/art.34458
71. Caplan A, Fett N, Rosenbach M, Werth VP, Micheletti RG (2017) Prevention and management of glucocorticoid-induced side effects: a comprehensive review: Infectious complications and vaccination recommendations. J Am Acad Dermatol 76:191–198. https://doi.org/10.1016/j.jaad.2016.02.1240
72. Hiraki LT, Feldman CH, Marty FM, Winkelmayer WC, Guan H, Costenbader KH (2017) Serious infection rates among children with systemic lupus erythematosus enrolled in medicaid. Arthritis Care Res 69:1620–1626. https://doi.org/10.1002/acr.23219
73. Singh JA, Hossain A, Kotb A, Wells G (2016) Risk of serious infections with immunosuppressive drugs and glucocorticoids for lupus nephritis: a systematic review and network meta-analysis. BMC Med 14:137. https://doi.org/10.1186/s12916-016-0673-8
74. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement (2000). Am J Respir Crit Care Med 161:S221-247. https://doi.org/10.1164/ajrccm.161.supplement_3.ats600
75. Kimura Y, Fieldston E, Devries-Vandervlugt B, Li S, Imundo L (2000) High dose, alternate day corticosteroids for systemic onset juvenile rheumatoid arthritis. J Rheumatol 27:2018–2024
76. Groot N, Heijstek MW, Wulffraat NM (2015) Vaccinations in paediatric rheumatology: an update on current developments. Curr Rheumatol Rep 17:46. https://doi.org/10.1007/s11926-015-0519-y
77. Sousa S, Duarte AC, Cordeiro I, Ferreira J, Goncalves MJ, Meirinhos T, Rocha TM, Romao VC, Santos MJ (2017) Efficacy and safety of vaccination in pediatric patients with systemic inflammatory rheumatic diseases: a systematic review of the literature. Acta Reumatol Port 42:8–16
78. Hoes JN, Jacobs JW, Boers M, Boumpas D, Buttgereit F, Caeyers N, Choy EH, Cutolo M, Da Silva JA, Esselens G, Guillevin L, Hafstrom I, Kirwan JR, Rovensky J, Russell A, Saag KG, Svensson B, Westhovens R, Zeidler H, Bijlsma JW (2007) EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 66:1560–1567. https://doi.org/10.1136/ard.2007.072157
79. Matoulkova P, Pavek P, Maly J, Vlcek J (2014) Cytochrome P450 enzyme regulation by glucocorticoids and consequences in terms of drug interaction. Expert Opin Drug Metab Toxicol 10:425–435. https://doi.org/10.1517/17425255.2014.878703
80. Buckley L, Guyatt G, Fink HA, Cannon M, Grossman J, Hansen KE, Humphrey MB, Lane NE, Magrey M, Miller M, Morrison L, Rao M, Byun Robinson A, Saha S, Wolver S, Bannuru RR, Vaysbrot E, Osani M, Turgunbaev M, Miller AS, McAlindon T (2017) 2017 American college of rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res (Hoboken) 69:1095–1110. https://doi.org/10.1002/acr.23279
81. Inoue Y, Mitsunaga K, Yamamoto T, Chiba K, Yamaide F, Nakano T, Morita Y, Yamaide A, Suzuki S, Arima T, Yamaguchi KI, Tomiita M, Shimojo N, Kohno Y (2018) Early use of alendronate as a protective factor against the development of glucocorticoid-induced bone loss in childhood-onset rheumatic diseases: a cross-sectional study. Pediatr Rheumatol Online J 16:36. https://doi.org/10.1186/s12969-018-0258-5
82. Baroncelli GI, Bertelloni S (2014) The use of bisphosphonates in pediatrics. Horm Res Paediatr 82:290–302. https://doi.org/10.1159/000365889
83. Le Jeunne C, Aslangul E (2013) Prolonged corticosteroid therapy and diet. Rev Med Interne 34:284–286. https://doi.org/10.1016/j.revmed.2012.11.014
84. Bloom BJ, Alario AJ, Miller LC (2011) Intra-articular corticosteroid therapy for juvenile idiopathic arthritis: report of an experiential

cohort and literature review. Rheumatol Int 31:749–756. https://doi.org/10.1007/s00296-010-1365-x
85. Jennings H, Hennessy K, Hendry GJ (2014) The clinical effectiveness of intra-articular corticosteroids for arthritis of the lower limb in juvenile idiopathic arthritis: a systematic review. Pediatr Rheumatol Online J 12:23. https://doi.org/10.1186/1546-0096-12-23
86. Ravelli A, Manzoni SM, Viola S, Pistorio A, Ruperto N, Martini A (2001) Factors affecting the efficacy of intraarticular corticosteroid injection of knees in juvenile idiopathic arthritis. J Rheumatol 28:2100–2102
87. Papadopoulou C, Kostik M, Gonzalez-Fernandez MI, Bohm M, Nieto-Gonzalez JC, Pistorio A, Lanni S, Consolaro A, Martini A, Ravelli A (2013) Delineating the role of multiple intraarticular corticosteroid injections in the management of juvenile idiopathic arthritis in the biologic era. Arthritis Care Res (Hoboken) 65:1112–1120. https://doi.org/10.1002/acr.21947
88. Ravelli A, Davi S, Bracciolini G, Pistorio A, Consolaro A, van Dijkhuizen EHP, Lattanzi B, Filocamo G, Verazza S, Gerloni V, Gattinara M, Pontikaki I, Insalaco A, De Benedetti F, Civino A, Presta G, Breda L, Marzetti V, Pastore S, Magni-Manzoni S, Maggio MC, Garofalo F, Rigante D, Gattorno M, Malattia C, Picco P, Viola S, Lanni S, Ruperto N, Martini A, Italian Pediatric Rheumatology Study G (2017) Intra-articular corticosteroids versus intra-articular corticosteroids plus methotrexate in oligoarticular juvenile idiopathic arthritis: a multicentre, prospective, randomised, open-label trial. Lancet 389:909–916. https://doi.org/10.1016/S0140-6736(17)30065-X
89. Eberhard BA, Sison MC, Gottlieb BS, Ilowite NT (2004) Comparison of the intraarticular effectiveness of triamcinolone hexacetonide and triamcinolone acetonide in treatment of juvenile rheumatoid arthritis. J Rheumatol 31:2507–2512
90. Zulian F, Martini G, Gobber D, Plebani M, Zacchello F, Manners P (2004) Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial. Rheumatology 43:1288–1291. https://doi.org/10.1093/rheumatology/keh313
91. Scott C, Meiorin S, Filocamo G, Lanni S, Valle M, Martinoli C, Martini A, Ravelli A (2010) A reappraisal of intra-articular corticosteroid therapy in juvenile idiopathic arthritis. Clin Exp Rheumatol 28:774–781
92. Job-Deslandre C, Menkes CJ (1990) Complications of intra-articular injections of triamcinolone hexacetonide in chronic arthritis in children. Clin Exp Rheumatol 8:413–416
93. Goldzweig O, Carrasco R, Hashkes PJ (2013) Systemic adverse events following intraarticular corticosteroid injections for the treatment of juvenile idiopathic arthritis: two patients with dermatologic adverse events and review of the literature. Semin Arthritis Rheum 43:71–76. https://doi.org/10.1016/j.semarthrit.2012.12.006
94. Gondwe JS, Davidson JE, Deeley S, Sills J, Cleary AG (2005) Secondary Cushing's syndrome in children with juvenile idiopathic arthritis following intra-articular triamcinolone acetonide administration. Rheumatology 44:1457–1458. https://doi.org/10.1093/rheumatology/kei154
95. Huppertz HI, Pfuller H (1997) Transient suppression of endogenous cortisol production after intraarticular steroid therapy for chronic arthritis in children. J Rheumatol 24:1833–1837
96. McKinney C, Sharma N, Jerath RS (2014) Livedoid dermatitis (Nicolau syndrome) following intra-articular glucocorticoid injection. J Clin Rheumatol 20:339–340. https://doi.org/10.1097/RHU.0000000000000146
97. Holland GN, Denove CS, Yu F (2009) Chronic anterior uveitis in children: clinical characteristics and complications. Am J Ophthalmol 147:667–678 e665. https://doi.org/10.1016/j.ajo.2008.11.009
98. Ravelli A, Martini A (2007) Juvenile idiopathic arthritis. Lancet 369:767–778. https://doi.org/10.1016/S0140-6736(07)60363-8
99. Angeles-Han ST, Lo MS, Henderson LA, Lerman MA, Abramson L, Cooper AM, Parsa MF, Zemel LS, Ronis T, Beukelman T, Cox E, Sen HN, Holland GN, Brunner HI, Lasky A, Rabinovich CE, Juvenile Idiopathic Arthritis Disease-Specific Uveitis Subcommittee of Childhood Arthritis Rheumatology Research A (2018) Childhood Arthritis and Rheumatology Research Alliance consensus treatment plans for juvenile idiopathic arthritis-associated and idiopathic chronic anterior uveitis. Arthritis Care Res (Hoboken). https://doi.org/10.1002/acr.23610
100. Bou R, Adan A, Borras F, Bravo B, Calvo I, De Inocencio J, Diaz J, Escudero J, Fonollosa A, de Vicuna CG, Hernandez V, Merino R, Peralta J, Rua MJ, Tejada P, Anton J (2015) Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. Rheumatol Int 35:777–785. https://doi.org/10.1007/s00296-015-3231-3
101. Constantin T, Foeldvari I, Anton J, de Boer J, Czitrom-Guillaume S, Edelsten C, Gepstein R, Heiligenhaus A, Pilkington CA, Simonini G, Uziel Y, Vastert SJ, Wulffraat NM, Haasnoot AM, Walscheid K, Palinkas A, Pattani R, Gyorgyi Z, Kozma R, Boom V, Ponyi A, Ravelli A, Ramanan AV (2018) Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative. Ann Rheum Dis 77:1107–1117. https://doi.org/10.1136/annrheumdis-2018-213131
102. Leinonen S, Immonen I, Kotaniemi K (2018) Fluocinolone acetonide intravitreal implant (Retisert((R))) in the treatment of sight threatening macular oedema of juvenile idiopathic arthritis-related uveitis. Acta Ophthalmol. https://doi.org/10.1111/aos.13744
103. Pichi F, Nucci P, Baynes K, Lowder CY, Srivastava SK (2017) Sustained-release dexamethasone intravitreal implant in juvenile idiopathic arthritis-related uveitis. Int Ophthalmol 37:221–228. https://doi.org/10.1007/s10792-016-0265-9
104. Ravelli A, Grom AA, Behrens EM, Cron RQ (2012) Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment. Genes Immun 13:289–298. https://doi.org/10.1038/gene.2012.3
105. Boom V, Anton J, Lahdenne P, Quartier P, Ravelli A, Wulffraat NM, Vastert SJ (2015) Evidence-based diagnosis and treatment of macrophage activation syndrome in systemic juvenile idiopathic arthritis. Pediatr Rheumatol Online J 13:55. https://doi.org/10.1186/s12969-015-0055-3
106. Aytac S, Batu ED, Unal S, Bilginer Y, Cetin M, Tuncer M, Gumruk F, Ozen S (2016) Macrophage activation syndrome in children with systemic juvenile idiopathic arthritis and systemic lupus erythematosus. Rheumatol Int 36:1421–1429. https://doi.org/10.1007/s00296-016-3545-9
107. Nakagishi Y, Shimizu M, Kasai K, Miyoshi M, Yachie A (2016) Successful therapy of macrophage activation syndrome with dexamethasone palmitate. Mod Rheumatol 26:617–620. https://doi.org/10.3109/14397595.2014.906053
108. Minoia F, Davi S, Horne A, Demirkaya E, Bovis F, Li C, Lehmberg K, Weitzman S, Insalaco A, Wouters C, Shenoi S, Espada G, Ozen S, Anton J, Khubchandani R, Russo R, Pal P, Kasapcopur O, Miettunen P, Maritsi D, Merino R, Shakoory B, Alessio M, Chasnyk V, Sanner H, Gao YJ, Huasong Z, Kitoh T, Avcin T, Fischbach M, Frosch M, Grom A, Huber A, Jelusic M, Sawhney S, Uziel Y, Ruperto N, Martini A, Cron RQ, Ravelli A, Pediatric Rheumatology International Trials O, Childhood A, Rheumatology Research A, Pediatric Rheumatology Collaborative Study G, Histiocyte S (2014) Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. Arthritis Rheumatol 66:3160–3169. https://doi.org/10.1002/art.38802