Glucocorticoid treatment in spondyloarthritis

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ABSTRACT

Spondyloarthritides (SpA) are chronic inflammatory rheumatic diseases that usually affect the axial skeleton and may involve entheses and peripheral joints. The main subtypes are ankylosing spondylitis (AS) and psoriatic arthritis (PsA). Other subtypes are reactive arthritis, arthritis associated with chronic inflammatory bowel diseases and undifferentiated axial and peripheral spondyloarthritis. Although SpA were regarded as variants of rheumatoid arthritis (RA) until the 1970s, it is now well established that the pathogenesis of SpA is quite different from that of RA.

There is a lack of good clinical studies on glucocorticoid therapy in the SpA. While there is no reasonable doubt that intraarticular local therapies in SpA are as effective as in RA and other forms of arthritis, the evidence for a systemic use is at best marginal. While very high doses may be effective in some patients with AS, the possible value of low-dose corticosteroid therapy in patients with PsA has never been well addressed, with respect to either clinical efficacy or inhibition of radiographic progression. Future studies are needed to clarify this important issue for usual patient care.

Introduction

Spondyloarthritides (SpA) are chronic inflammatory rheumatic diseases that usually affect the axial skeleton and may involve peripheral joints and entheses. The main and most frequent subtype of SpA is ankylosing spondylitis (AS), followed by psoriatic arthritis (PsA) and other subtypes: reactive arthritis, arthritis associated with chronic inflammatory bowel diseases and undifferentiated (1) axial (2) and peripheral (3) spondyloarthritis. The pathogenesis of SpA has been shown to be largely associated with patient genotype (4), with the strongest association known to HLA B27 (5). Inflammation leading to osteodestructive and/or osteoproliferative changes are most characteristic in patients with SpA in different patterns: while patients with AS are characterised by new bone formation and ankylosis of the sacroiliac joints and the spine, patients with PsA more often show erosive changes in peripheral joints (6).

Glucocorticoids are clearly known to be effective in the treatment of patients with RA (7). By contrast, their role in the treatment of SpA is less clear, since little clinical data are available to support their use, especially in patients with AS. Since there is evidence that pathogenesis of RA and AS is quite different (see *Clin Exp Rheumatol* 2009, Supplement 55), it is not surprising that some drugs appear to have different levels of effectiveness (8) – potentially as a result of different expression of the glucocorticoid receptor on the cell membrane of patients with SpA compared to those with RA (9-11).

Glucocorticoids are used extensively and are rather efficacious in the treatment of most inflammatory rheumatic diseases (see other articles in this supplement). On that background, it seems remarkable that only a few clinical trials on the use of oral corticosteroids have been performed in patients with AS and PsA. Therefore, the use of systemic glucocorticoids is not supported by current management recommendations for patients with SpA (12-16), primarily because not a single placebo-controlled study has been performed in patients with SpA to document their efficacy. However, given clinical evidence that glucocorticoid treatment is effective in some individual patients with SpA as published in case reports, further studies and a characterisation of subgroups that may respond better to this treatment will be of value to an improved approach to future therapeutic strategies in SpA.

Overview of the effects of glucocorticoids in the different subtypes of SpA

Ankylosing spondylitis

Only a few trials have been reported on systemic administration of glucocorti-

coids in patients with AS, published in the 80s and 90s, in which intravenous pulse therapy with methylprednisolone was given to patients with an insufficient response to NSAIDs (17-21). However, these studies have included only a small number of patients and the doses given was rather high.

In a study comparing two doses of methylprednisolone pulse therapy (*i.e.* 1000 mg (n=8) *vs.* 375 mg (n=9) administered intravenously once daily for 3 consecutive days), patients in the higher dosage group remained in a relatively good condition for about one year, and relapsed to their baseline status of pain about 100 days later than in the comparator, lower-dosage group. However, this difference was not statistically significant and the study did not include a placebo group (17).

Two papers reported a remarkable effect of methylprednisolone in HLA-27-negative AS patients (20, 21). Female patients may show better responses to glucocorticoid therapy in comparison to male patients with AS and axial involvement (J. Braun, unpublished observation) but this has not been addressed in a clinical trial.

A few studies on the intraarticular application of corticosteroids into peripheral and sacroiliac joints in AS have been reported (22-26). In Germany, an intraarticular application of corticosteroids, unguided or guided by ultrasonography, is frequently used in patients with monoarthritis or oligoarthritis. Superior results of local administration of corticosteroids in patients with sacroiliitis when guided by computed tomography or similar imaging procedures are reported (24). Thus, a CT-guided application of 40 mg triamcinolonacetonide into the sacroiliac joints of 30 patients showed a positive effect in about 80% of patients, maintained over about 9 months (23-25). In one study, improved status with treatment was confirmed by MRI examinations during follow-up: a decrease of subchondral bone marrow oedema was seen in 90% of the patients after 3 months (24). In summary, CT-guided local therapy of sacroiliitis with corticosteroids appears clinically efficacious on a short- and on a mid-term basis. Of note, the decrease of pain lasted significantly longer with the guided rather than "blind" injection (26).

Taken toegther, while local treatment witth glucocorticoids seems to work for patients with AS, the systemic therapy does not seem to be useful.

Psoriatic arthritis (PsA)

No controlled data from randomised clinical trials are available on the systemic use of glucocorticoids in PsA. Dermatologic expert opinion often includes recommendations to avoid the systemic use of corticosteroids, not only because of the rapid worsening after withdrawal of therapy (27), but also because of possible negative effects on psoriatic skin lesions. Such effects may lead to a decreased efficacy of standard treatment regimens such as with methotrexate and cyclosporine (28).

Nevertheless, many rheumatologists have used low-dose prednisolone for the treatment of PsA with clinical benefit. Accordingly, in a multicentre study with 180 patients performed in the 1960s, treatment with glucocorticoids was reported in 24.4% of the patients (29).

No data have been reported on glucocorticoid treatment of patients with axial involvement associated with psoriasis. However, sacroiliac injections have been recommended analogous to those in patients with AS discussed above (30), although little data other than case reports (31) are available concerning intraarticular glucocorticoids in patients with PsA. In patients with dactylitis and enthesitis, high dosages of glucocorticoids given systemically or locally have shown some effect (32, 33). There are also no data on patients with SAPHO syndrome but many of those patients are treated with glucocorticoids (34).

Taken together, glucocorticoids given locally or systemically seem to be useful at least for some patients with PsA.

Reactive arthritis (ReA)

Similar to PsA, controlled data that support the use of glucocorticoids in ReA are not available. In a report based only on expert opinion, the use of glucocorticoids has been recommended for patients with ReA, but only when severely affected. After starting with a relatively high dosage of 30-40 mg of prednisolone, a fast reduction and complete withdrawal within only a few months have been proposed (35). Our own experience indicates that relatively high dosages of glucocorticoids in the range of of 1mg/kg may be needed in patients with high disease activity including fever and strongly elevated CRP levels; this includes patients diagnosed with "Reiter's syndrome" – an eponymous term now used rarely, as use of the name has been discouraged already some years ago (36).

Taken together, glucocorticoids given locally or systemically are useful for the treatment of ReA.

Arthritis associated with chronic inflammatory bowel diseases (IBD)

There are no data for the use of glucocorticoids in patients with arthritis associated with IBD. However, clinical experience indicates that joint symptoms generally improve after treatment of the gastrointestinal disease with glucocorticoids and/or immunosuppressive agents (37). Two types of arthritis associated with IBD have been described.

Responses to glucocorticoids are more likely to occur in parallel to gastrointestinal symptoms in patients with oligoarticular peripheral arthritis type I, which is more closely associated with the disease activity of the bowel disease. The other polyarticular form of peripheral arthritis, known as type II, usually behaves differently, tending not to fluctuate closely with the course of the bowel disease. Glucocorticoid treatment of type II arthritis is largely orientated to the arthritic symptoms. In our experience, medium doses of glucocorticoids given systemically provide symptom relief. Our experience is that local glucocorticoid therapies are effective in patients with (spondylo)arthritis associated with IBD - as in other forms of SpA.

Recommendations for the treatment of AS in association with inflammatory bowel disease are based on the general management of the underlying bowel disease and local therapies such as injection of joints including the sacroiliac joint (37, 38). The treatment is in general rather symptom-oriented, due in part to the fact that these forms of arthritis are only rarely erosive.

Taken together, arthritic symptoms do fluctuate with bowel symptoms in Type 1 but not in Type 2 arthritis associated with IBD. However, glucocorticoids are useful in both types.

Anterior uveitis

Patients with acute anterior uveitis or iritis are treated efficaciously with local glucocorticoids (39-42). Timely local use of glucocorticoids shortly after the occurrence of first symptoms has shown an especially favourable clinical efficacy. Severe cases may require the systemic use of glucocorticoids. No data from randomised placebo-controlled trials are available, and are unlikely ever to be available, as placebo treatment is ethically inappropriate because irreversible damage of the affected eye leading to blindness may occur in untreated patients.

Taken together, glucocorticoids are effective in the treatment of anterior uveitis both locally and systemically.

Summary

Although frequently used, there is a striking lack of data from clinical trials or observational studies concerning the use of glucocorticoids in SpA. However, clinical experience and expert opinion indicate that local application of glucocorticoids has similar efficacy as in other inflammatory rheumatic diseases such as RA and osteoarthritis.

The indications for a systemic use of glucocorticoids in the different forms of SpA are less clear.

In AS, the systemic use of glucocorticoids for the treatment of axial symptoms is frankly discouraged (13), although our personal experience indicates responses in patients with peripheral arthritis – but, again, data are lacking.

German rheumatologists do use glucocorticoids for the treatment of PsA (43), although data are lacking. Dermatologists usually discourage the use of glucocorticoids because the skin disease may worsen substantially after withdrawal.

The prognosis of ReA is generally favourable but systemic glucocorticoids may be needed initially in patients with high disease activity. Some weeks or months later tapering and discontinuation is usually possible.

In SpA associated with IBD, treatment is directed primarily at the underlying bowel disease, and joint symptoms usually improve on that basis. Patients with peripheral arthritis Type II, which occurs rather independently of the gut symptoms, are treated on a symptom-oriented basis, often with glucocorticoids.

Treatment of acute anterior uveitis with local glucocorticoid therapy is usually sufficient, but severe cases may require systemic application of high doses of glucocorticoids.

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