Therapies for Axial Disease in Psoriatic Arthritis. A Systematic Review

PETER NASH

ABSTRACT. Prevalence rates for axial involvement in psoriatic arthritis (PsA) vary from 40% to 74% depending upon criteria for diagnosis. In the absence of trial evidence to assess axial involvement in PsA, the GRAPPA group, by consensus, has suggested that outcome measures and therapies for axial disease in ankylosing spondylitis (AS) be used. This systematic review addresses the management of axial disease in PsA, and provides treatment recommendations based on the AS literature. (First Release May 15 2006; J Rheumatol 2006;33:1431–4)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS PSORIATIC ARTHRITIS AXIAL DISEASE
SPONDYLOARTHROPATHY PSORIASIS ANTIRHEUMATIC THERAPY

INTRODUCTION

Axial disease in psoriatic arthritis (axPsA) is common; prevalence rates range from 40% of PsA patients if inflammatory spinal pain is used as the diagnostic criteria, to 78% if radiologically defined sacroiliitis is required[1]. Despite shared features between axial disease in PsA and ankylosing spondylitis (AS), important distinctions have been described:

- Reduced male preponderance
- Less overall disease severity
- Less severe sacroiliitis
- Less syndesmophyte development (e.g., "spotty" asymmetric distribution of marginal and paramarginal syndesmophytes with random progression)
- Less cervical involvement
- Better preservation of spinal mobility
- Relative absence of ligamentous ossification
- Relative sparing of apophyseal joints
- Reduced association with HLA-B27 positivity (prevalence rates from 21% to 76% with a strong association when positive with sacroiliitis)[2-4]

These observations, however, are based upon studies of small patient populations either assessed retrospectively or followed prospectively for relatively short periods[2-4].

Outcome Measures

Outcome measures used in the assessment of AS have not been validated in PsA, and assumptions of equivalent utility may be false. For example, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores were significantly lower in PsA than in AS and correlated poorly with external indicators of disease activity[5]. In addition, spinal assessments have shown poor sensitivity and specificity for sacroiliac joint measures, including Schober's test and its modifications, chest expansion, cervical range of movement, and sacroiliac joint tenderness. Sensitivity to change and minimal clinically significant differences have not been established[6].

Outcome measures in axPsA are under active assessment; however, the Assessments in Ankylosing Spondylitis (ASAS) Working Group has developed response criteria for improvement in AS, and by consensus, these will be used in this review[7]. ASAS has validated composite measures measuring disease activity (BASDAI), function (Bath AS Functional Index, BASFI), patient global assessment (Bath AS Global Index, BASGI), and spinal mobility (Bath AS Metrology Index, BASMI). Structural damage is evaluated using validated radiographic instruments (Bath AS Radiology Index/Stoke AS Spine Score, BASRI/SASSS)[7].

Search Strategy

A literature search of Medline, EMBASE, CINHAL, and the Cochrane Library from 1966 to 2005 was done using the key MeSH terms ankylosing spondylitis, psoriatic arthritis, axial disease, spondyloarthropathy (SpA), psoriasis, spondylitis, and antirheumatic therapy, alone and in combination, and of the following terms with PsA, SpA, or spondylitis: salazopyrine, methotrexate, physiotherapy, pamidronate, gold oral and intramuscular, azathioprine, cyclosporine, hydroxychloroquine, infliximab, etanercept, adalimumab, and tumor necrosis factor (TNF).

The resulting database was culled for articles specifically addressing axial disease and its therapy in psoriasis, PsA, AS, or SpA. Abstracts from annual meetings of the American College of Rheumatology and the European Congress of Rheumatology were admitted as evidence if sufficient detail was available to determine level of evidence.

RESULTS

Physiotherapy — Level of Evidence 1a, Grade A

In a review of 6 trials of physiotherapy in AS (561 participants), supervised group physical therapy significantly

From the Department of Medicine, University of Queensland, Cotton Tree, Australia.

P. Nash, MBBS (Hons), FRACP.

Address reprint requests to Dr. P. Nash, Department of Medicine, University of Queensland, PO Box 59, Cotton Tree, Australia.
E-mail: pnash@tpg.com.au

improved global health and functioning, pain, and stiffness compared with home-based individual exercise[8]. In 2 trials, individualized home exercise programs had greater effects on spinal mobility and physical function, compared with no intervention. In 3 trials, supervised group physiotherapy produced better patient global assessments, compared with home-exercise programs. In another study, 3 weeks of inpatient spa-exercise therapy followed by 37 weeks of weekly outpatient group physiotherapy (without spa) showed evidence for effects on pain, physical function, and patient global assessment, compared with outpatient group physiotherapy alone. An additional trial of a home-based exercise and disease education package showed benefit for spinal mobility and function in AS[9].

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAID) appear to be rapidly efficacious in relieving signs and symptoms of pain and morning stiffness (level of evidence 1a, grade A) in axial disease. Continuous NSAID usage can reduce radiological progression (level of evidence 1b, grade A), although separate treatments for inflammation and progression of structural damage have been suggested[10].

Coxibs may have fewer gastrointestinal side effects, but cardiovascular issues may nullify that benefit. Equivalent efficacy has been demonstrated for one coxib[11], and superior efficacy over 12 months for etoricoxib over a nonselective NSAID (naproxen) has been shown (level of evidence 1b, grade A)[12]. Two NSAID at maximum recommended/tolerated and continuous doses are recommended before concluding that a patient is NSAID refractory (level of evidence 4, grade C).

Simple Analgesia

No disease-specific evidence supports paracetamol or other analgesics in axial disease of AS or PsA.

Corticosteroids

Significant benefit has been noted with intraarticular glucocorticoids for active peripheral arthritis (level of evidence 4, grade C) and given under fluoroscopic or computer tomographic guidance into the sacroiliac joints (level of evidence 1b, grade A). A dose-response, double-blind comparison of 1 g versus 375 mg of methylprednisolone given as 3 consecutive daily intravenous (IV) infusions demonstrated no significant differences[13]. Open studies evaluating pulse IV methylprednisolone 1 g for 3 consecutive days have demonstrated prompt improvement lasting 3–21 months (level of evidence 2b, grade B)[14].

Disease Modifying Antirheumatic Drugs

Sulfasalazine (SSZ). Sulfasalazine has been studied in PsA, but only small percentages of patients had axial involvement, and responses were poorly documented. In a review of 12 controlled trials of SSZ, improvement in erythrocyte sedimentation rate (ESR) and morning stiffness favored SSZ over placebo (level of evidence 1a, grade A)[15]. In the largest and longest of these trials (221 patients, 36-week course)[16], improvement was significant ($p = 0.01$) but modest, with 55% and 45% improvements in the PsA response criteria for SSZ and placebo, respectively. The action of SSZ appears to be confined to peripheral arthritis with no evidence of benefit in axial disease (level of evidence 1a, grade A).

A single trial evaluated SSZ in primary outcome analyses of back pain, chest expansion, occiput-to-wall test, and patients' general well-being. Compared with other trials, patients in this study had more peripheral arthritis and the highest level of baseline ESR, but the shortest disease duration. Withdrawals for side effects with SSZ were significant. Spondylitis was not improved, and radiological progression was not retarded with SSZ[16].

Oral formulations of 5-ASA (pentasa and asacol) have been examined in open trials in AS without benefit[17].

Methotrexate (MTX). The efficacy of MTX in PsA was first described in 1964, but benefit has not been demonstrated in axial disease (level of evidence 1a, grade A). A 3 month, double-blind, placebo-controlled study of parenteral MTX in 21 patients who had active skin disease and peripheral arthritis showed significant improvement in joint tenderness and range of motion, extent of skin involvement, and ESR[18].

In a randomized, double-blind, placebo-controlled trial comparing oral low dose pulse MTX with placebo, the only significant response was the physician assessment of arthritis activity[19]. In a 24-month study of 38 patients, MTX did not show improvement in radiographic progression compared with matched controls[20].

In a randomized, double-blind placebo-controlled trial of 70 patients with AS, MTX showed significant benefit over 24 weeks in physical well-being, BASDAI, BASFI, physician global assessment, patient global assessment, spinal pain, and Health Assessment Questionnaire for Spondyloarthropathies (HAQ-S) (level of evidence 1b, grade A)[21].

The toxicity, particularly hepatotoxicity, of MTX in psoriasis and PsA has been compared with that in RA. A retrospective study of 104 patients followed over 2 decades did not suggest increased toxicity[22]. However, analysis is difficult: studies tend to be retrospective, with no controlling for alcohol consumption; older studies include daily therapy; and many do not include folic acid supplementation. No consensus exists as to the indications for liver biopsy either before treatment or at specified intervals during treatment.

Gold salts and antimalarial drugs. Anecdotal case reports have shown no benefit for gold salts and antimalarial drugs in axPsA[23,24].

Azathioprine. Azathioprine was associated with a low response rate and a high withdrawal rate due to adverse effects[25].

Thalidomide (level of evidence 3, grade B). A one-year, open-label trial of thalidomide was conducted in 30 men with treat-

ment-refractory AS. Of 26 patients who completed the study, 80% showed > 20% improvement in 3–6 months; 9 patients became pain-free. Peripheral neuropathy and teratogenicity remain major limitations[26].

Leflunomide (level of evidence 1b, grade A for non-benefit). A randomized, placebo-controlled, 6-month trial of leflunomide in 45 patients with AS showed no significant benefit, and axial disease was not assessed[27].

Cyclosporine (level of evidence 3, grade B). A review of 16 studies of cyclosporine therapy in PsA showed improvements in rash and peripheral arthritis, without evaluating axial disease[28]. The addition of cyclosporine to MTX nonresponders significantly improved peripheral joint scores, but axial disease was not evaluated[29].

Bisphosphonates (level of evidence 1b, grade A). One randomized, controlled, single-center study and 2 open analyses examined IV pamidronate in NSAID-refractory AS patients. In a 6-month, double-blind, dose-response comparison, 60 mg had significant benefit over 10 mg IV pamidronate; 40% of patients had a 50% BASDAI reduction, but no significant reduction in peripheral pain[30].

Biological Therapies

Interleukin 1 receptor antagonist anakinra (level of evidence 3, grade B). An open-label, 3-month pilot study of anakinra in 9 patients showed significant improvements in ASAS 20% response (BASFI, BASDAI, AS Quality of Life, C-reactive protein, and ESR), and significant improvement in enthesitis and osteitis lesions as measured by magnetic resonance imaging (MRI)[31].

Anti-TNF therapy. Trial evidence shows etanercept, infliximab, and adalimumab provide significant improvement in disease activity, range of motion, physical function, and quality of life, both as monotherapy and as add-on therapy to other disease modifying antirheumatic drugs in both psoriasis and PsA[32-40]. All 3 agents retard radiologic progression in PsA. Axial disease was not studied, as too few patients had spondylitis. In AS trials, few patients had psoriasis (5–15%), and ASAS 20 responses were inferior in this subset.

Etanercept trials in PsA and AS showed improvements in symptoms and signs of disease, mobility, physical function, and acute phase reactants, with complete resolution or improvement noted in 86% of lesions, documented by MRI, in the AS trial (level of evidence 1a, grade A)[32-34].

Infliximab trials in PsA have shown significant response in NSAID-refractory patients (those with long-standing, severe disease), and benefit was maintained up to 24 months with continued therapy (level of evidence 1a, grade A)[35-37].

Adalimumab therapy in 315 PsA patients treated for 6 months showed significant improvements in joint and skin manifestations, improved quality of life, and retardation of radiological progression (level of evidence 1b, grade A). Only one patient in this study, however, had axial disease[38-40].

TREATMENT RECOMMENDATIONS AND CONCLUSIONS

Validated outcome measures and formal trials in adequate numbers of patients with axPsA are urgently needed to address the safety and efficacy of treatments for axPsA. At present, the ASAS specifications and definitions for diagnosis, assessment of disease, treatment failure, treatment contraindications, and assessment of response are recommended and are summarized as follows:

Treatment Algorithm[41,42]

1. Establish diagnosis of PsA.
2. Initiate therapy with physiotherapy and continuous NSAID for clinically symptomatic axial disease.
3. Consider corticosteroid injection to symptomatic sacroiliac joint.
4. If axial disease is persistent, particularly with radiological evidence, commence anti-TNF therapy, with attention to contraindications and appropriate monitoring.
5. Other considerations include methotrexate (with appropriate monitoring) or pamidronate (intravenous infusions).

Until further evidence is available, infliximab, etanercept, and adalimumab are suggested for reduction of signs and symptoms of moderate to severely active axPsA in patients with an inadequate response to at least 2 NSAID. Either SSZ or MTX are suggested in patients with predominantly active peripheral arthritis.

Efficacy, effect size, and number needed to treat have been recently reviewed[42]. As trial evidence becomes available in patients with PsA with specific axial involvement, these recommendations can be reviewed without the necessity of using AS surrogates.

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