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TASMAN MEDICAL JOURNAL
ISSN 2652-1881
Volume 3 (1): 11-16; (2021)

FIONA STANLEY HOSPITAL AND SOUTH METROPOLITAN HEALTH SERVICE (PERTH, AUSTRALIA) SPECIAL EDITION

RESEARCH

An audit of clinical service delivery and outcomes in diffuse idiopathic skeletal hyperostosis – preliminary evidence for efficacy of tumour necrosis factor inhibition therapy

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Key Words
Diffuse idiopathic skeletal hyperostosis; TNF inhibitors; ankylosing hyperostosis; spondylo-arthritis; ankylosing spondylitis

Abstract
Objectives Diffuse idiopathic skeletal hyperostosis (DISH) is a common spinal disorder for which there is no specific drug treatment. The aim of this data audit was to determine the outcome of therapy with tumour necrosis factor inhibition (TNFi) in painful DISH.
Methods We performed a retrospective audit of patients with DISH followed from 2006 to 2020. Twelve patients with painful DISH who had a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of 6 or higher at outset, who had been treated empirically with a TNFi after failed treatment with exercise, NSAID/Coxibs and/or non-opiate analgesics were compared with 7 patients with DISH (BASDAI < 6 at onset) observed whilst receiving standard of care, but not TNFi.
Results One TNFi-treated patient was intolerant of TNFi. Eight patients had a 2-point or greater reduction in disease activity in the BASDAI measure. This is similar to the clinical response observed in patients with TNFi-treated ankylosing spondylitis in clinical trials. Based on intention to treat, the response rate was 67%. In contrast, only 1 of the 7 untreated DISH patients had a 2-point improvement in BASDAI (14%).
Conclusions These results support the efficacy of TNF inhibition in painful DISH. Based on these uncontrolled results we conclude that a formal prospective trial of the safety and efficacy of TNFi in DISH is justified.
Tasman Medical Journal 2021: 3 (1); 11-16

Introduction

Diffuse idiopathic skeletal hyperostosis (DISH), also known as Forestier's disease or ankylosing hyperostosis, is a common skeletal disorder, which is reported to range in frequency from 3.8% of males and 2.6% of females in a Finnish population-based study to 22.4% of males and 13.4% of females in an Israeli hospital-based study.[1, 2] The disorder was first described by Forestier, Jacqueline and Rotes-Querol in 1950.[3] The skeletal phenotype suggests it is an historically ancient disorder, but the pathophysiology is still poorly understood. Paleoradiological studies confirm the antiquity of the disease and raise the possibility of

familial clustering, which, in turn, suggests a genetic contribution to the aetiology.[4]

DISH is characterised by irreversible calcification and ossification of the spinal ligaments and entheses. Although clinically similar to spondyloarthropathies, the two disorders can be distinguished on the basis of their immunogenetic profile and imaging signs, especially in respect to the sacro-iliac (SI) joints, which are characteristically spared in DISH.[5] Clinically, the spinal manifestations overlap considerably, but in the periphery, there are important differences, most notably the absence of inflammatory arthritis in DISH.

Both DISH and ankylosing spondylitis (AS) are characterised by spinal pain and entheseal lesions that may have common inflammatory components, which could explain the shared responsiveness to non-steroidal anti-inflammatory drugs (NSAID). Several groups of investigators have reported inflammatory changes in the spine and SI joints in patients with symptomatic DISH who required MRI for diagnostic assessment.[6-8] These changes include bone marrow oedema (BMO) lesions, especially at the vertebral corners and sometimes in relation to the SI joints. In contrast, bone erosions in the vertebrae and SI joints do not occur in DISH. Whether the BMO lesions diminish or resolve, either with time or treatment, is not yet known. Furthermore, whether any of those patients deemed to have non-radiographic spondyloarthritis in other studies[9,10] that have demonstrated TNFi responsiveness may have included patients with early or established DISH warrants closer examination.

HLA B27 is not increased in DISH, whereas in AS it occurs in approximately 90% of patients with classical imaging.[11, 12] There is conjecture as to whether DISH is a painful condition, with the weight of evidence suggesting that pain is absent more often than not.[13-16] However, patients with DISH who attend tertiary referral centres, or who are referred to rheumatologists, frequently have severe pain, which is otherwise difficult to explain, while some have incapacitating pain which can interfere with daily life and work performance or be work-disabling.[14] Although traditionally considered a non-inflammatory, "degenerative" disorder of the spine, the pain in DISH is often at least partially relieved by NSAIDs. Recent imaging studies utilising magnetic resonance imaging (MRI) have reported inflammatory lesions in the vertebrae of persons with DISH.[6-8] Collectively, these observations raise the possibility that, at least in a subset of patients with DISH, there may be a significant inflammatory component and in turn, a potential to respond to tumour necrosis factor inhibition or other biologic or targeted synthetic DMARD therapies.

We report an uncontrolled audit of pain and function over time in patients with DISH referred to a tertiary centre and treated or not treated with a TNFi on the basis of the BASDAI score.

Methods

We examined the medical records of 19 patients with DISH who attended our outpatient clinic over a 14-year period (2006 to 30th June 2020 inclusive). Patients were identified by physician recall and a word search of clinic letters from hospital and rural clinics and private practice clinics. Each case was diagnosed by a physician on the basis of clinical and radiological findings. Patients were treated with various TNF inhibitors according to defined criteria: 1) Spinal pain for at least 3 months and refractory to exercise in combination with NSAIDS and/or non-opiate analgesics. 2) BASDAI greater than 6.0

	Treated	Untreated
N	12	7
% male	83	100
Age median, (range)	63(43-74)	57(50-83)
BASDAI score at entry (median)	7.4	5.5
Years of Tx/observation mean (SD)	4.0(3.2)	3.6(1.1)
Radiological Grade mean (SEM)	2.8 (0.2)	2.5 (0.3)
Sacroiliitis	0	1
HLA B27	2 (of 11)	0 (of 5)

Table 1. Demographic, clinical and radiological characteristics of DISH patients according to treatment using various TNF inhibiters (see text). Tx = treatment, SD = standard deviation, SEM = standard error of the mean.

Radiological criteria for DISH were used for classification purposes. Two musculoskeletal radiologists (WHB and SJS) evaluated digital imaging of the spine and SI joints. Images were available in 14 of the 19 patients. Where there were discrepancies in grading or assessment, agreement was reached by review and consensus. The criteria described by Fornasier, Littlejohn and Urowitz[17] who obtained and analysed data from an autopsy study, were utilised for classification. Based on these radiological criteria, patients were classified as mild (score = 1), moderate (score = 2) or severe (score = 3). Patients were also evaluated for changes characteristic of inflammatory sacroiliitis.

Since no validated clinical assessment tool exists for symptomatology in DISH, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[18] was

deemed to be an acceptable surrogate index and used here as the primary outcome metric. When BASDAI was determined, patients were blinded to all preceding assessments. A single physician administered the BASDAI questionnaire utilising standard instructions. Responses to treatment and progress were determined by serial BASDAIs. These were audited over time and plotted for comparison. BASDAI results over the duration of the study were available for about 85% of the time periods of relevance. HLA B27 was determined in 16 of the 19 participants.

All data analysed were collected as part of routine diagnosis and treatment.[19] The retrospective analysis was of outcomes in both untreated and treated patients. The study data are totally anonymous.

Statistical analysis

Medians, confidence intervals, frequencies of findings and statistical comparisons were applied to patient age, treatment duration and radiological grades utilising the online Graphpad Quickcalcs® program.[20]

Ethics

Ethical approval was not required according to the Western Australian Health Research Governance Policy and Procedures: Exemption from Ethical and Scientific Review.[21] These policies are in accordance with the Australian National Statement on Ethical Conduct in Human Research.[22] This audit is registered with Australian New Zealand Clinical Trials Registry, reference number ACTRN12617001299392.

Results

Nineteen patients with DISH were identified and audited. Twelve patients satisfied the criteria for TNFi treatment, and 7 for no TNFi treatment (standard of care). Three patients came from a rural centre, the other 16 had an urban address. The demographic, clinical and radiological characteristics are shown in Table 1. A majority (89%) of the patients were male (10 of 12 TNFi-treated patients and all 7 untreated patients). The age range was 43 to 83y, with a median of 59y. The median ages of the treatment groups were 63y (treated) and 57y (untreated).

Comparable radiological severity scores were observed in the two treatment groups as shown in Table 1. The differences were not statistically significant (unpaired t-test). Radiological characteristic inflammatory sacroiliitis was present in 1 patient, who had not received TNFi. HLA B27 positivity was noted in 2 of 11 TNFi-treated DISH patients (18%) compared with 0 of 5 HLA-typed patients in the untreated group. The frequency of B27 in the whole cohort was 2 of 16 (13%), which accords with that in healthy Caucasian populations (10%)[23] and is similar to that in a local population from the town of Busselton in Western Australia, where 14 of 200 members (7%) of the population typed were B27 positive (personal communication, Dr Jack Bourke, Fiona Stanley Hospital). The difference between the untreated and treated cohorts was not statistically significant (p=0.49).

Serial BASDAI data is shown for the untreated and TNFi treated patients in Figure 1.

Results in TNFi-treated patients

TNFi drugs were offered to patients who had high and sustained BASDAI scores (more than 2 consecutive BASDAIs ≥6 at baseline). The median duration of therapy was 3.25 y (range 0.5 to 12.5 y). Eleven patients were treated for longer than 6 months and, in 5 cases, for more than 4 years. The prescribed agents were: etanercept (ETA), 6; adalimumab (ADA), 2; certolizumab (CERT), 4; golimumab (GOL), 1; infliximab (INX), 1.

One patient could not tolerate the TNFi (CERT) due to a rash that resolved promptly on cessation. He was deemed to have failed treatment on the intention to treat analysis (ITT). Eight of the remaining 11 patients responded to TNFi with sustained falls in the BASDAI > 2 points (Figure 1). When the nadir in BASDAI was compared to baseline in the TNFi treated group, the fall was statistically significant (p=0.003, paired t test)

When the treated group was compared to the observed group, the difference in baseline to nadir for the two groups was marginally significant (3.51 vs 0.54, p=0.047, unpaired t test).

A sharp reduction was seen during the first 2 years of treatment in 8 patients whose response was clinically unequivocal. Reductions in BASDAI were unrelated to radiologic classification grade. One patient developed a serious infection (pneumonia requiring hospitalisation) during the 60 patient-years (PY) of TNFi exposure (1.67/100 PY). This is similar to the corresponding rate in AS (1.3/100 PY, CI 0.9 to 2.0).[24]

Partial deterioration was observed in 2 of the 8 TNFi treated definite initial responders after 4y. Both were receiving ETA. One has since stabilised and continues with ETA. The other stopped treatment because of uncertainty over efficacy. He then deteriorated sharply, but responded again when the same TFNi (ETA) was restarted.

Three patients have been treated long-term. They had a baseline BASDAI of 7.0, 7.5 and 6.4. The most recent

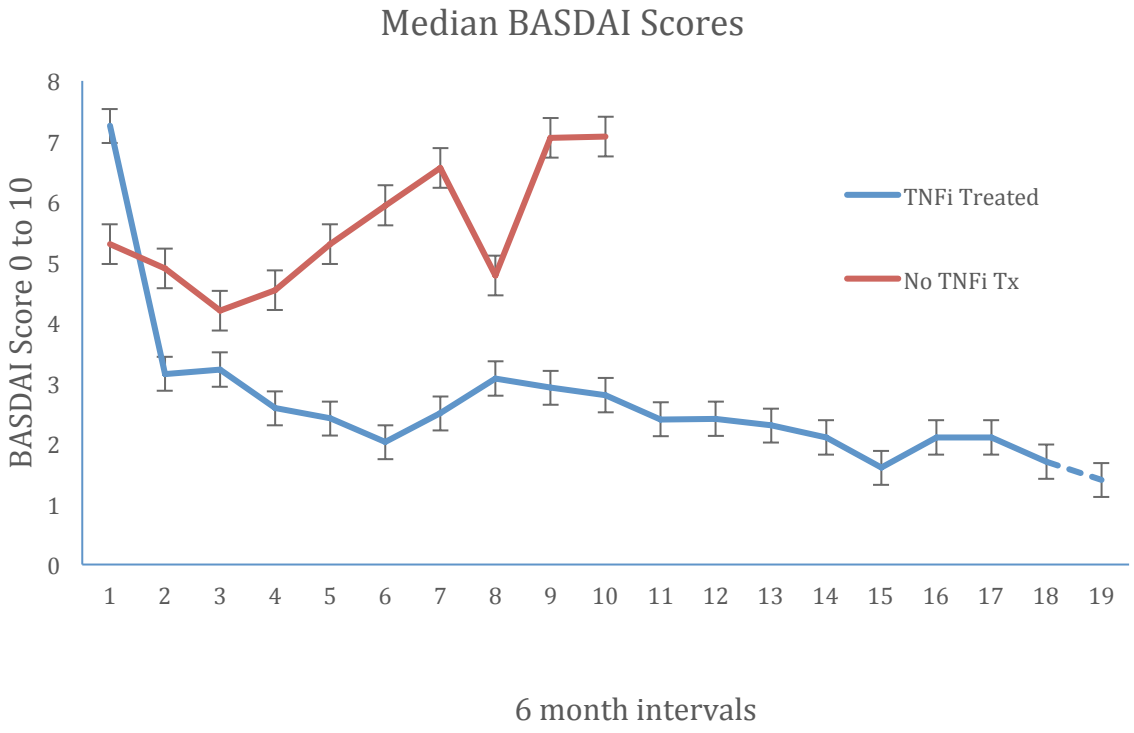

Fig. 1. Median (error bars denote SEM) BASDAI scores over time in untreated diffuse idiopathic skeletal hyperostosis (DISH) (orange, n = 7) and TNFi treated DISH (blue, n = 12). Solid line represents the mean of 3 or more observations; dashed line represents the mean of fewer than three values. Tx = treatment. Time point 1 denotes baseline.

BASDAI scores were 0.38, 2.48 and 0.76 respectively at 8, 10 and 7.5y of follow-up.

Results in untreated patients

The median duration of observation in the untreated DISH patients was 3.5y, range 2-5y. All but 1 of the 7 untreated DISH patients remained stable or progressively deteriorated. Their median initial and final BASDAI scores were 5.3 and 7.1 (Figure 1). One of the 7 (14%) untreated DISH patients had spontaneous improvement (2-point decrease in BASDAI).

Discussion

In this report, we provide retrospective and uncontrolled data, from 16 years of observation, which indicates that nearly 70% of patients with painful DISH and BASDAI > 6 appear to improve when treated with a TNFi. Compared to published reports, the observed responses were similar to those seen in AS where TNFi therapy now represents a therapeutic benchmark.[25] The falls in BASDAI were slower and not quite as marked as in AS. In apparently unequivocal responders (67% of those treated) the, responses were well sustained (0.5 to 12.5y), militating against a placebo effect. Spontaneous improvement or statistical regression to the mean however, are not definitely excluded, but appear unlikely. BASDAI reductions were not agent-specific, indicating a class effect of TNFi as in AS. The treatment was well tolerated.

One possible explanation for these results is the presence of an unrecognised TNF-mediated inflammatory component to DISH, as in AS, possibly associated with bone marrow oedema. We did not have sufficient magnetic resonance (MR) images to assess this possibility adequately, but MR imaging will be important in future studies. Another possible explanation is a TNFi-mediated, non-specific reduction in pain. This cannot be discounted, but pain in other arthritides, for example hand osteoarthritis, is not reduced by TNFi.[26] Nevertheless, there may be important differences in respect to the pain generators in these disorders, so caution is required. A third possibility is that the response to TNFi may be due, at least in part, to psychometric factors, particularly anxiety/depression, which may coexist with chronic pain in longstanding and severe DISH and other disorders.[27]

The strengths of this study encompass the inclusion of clinically and radiologically well characterised DISH participants and the exclusion of patients with known spondyloarthropathies as well as the relatively long period of observation in treated and untreated participants alike. Perhaps most importantly, the audit

has allowed a potential class of therapy to be identified, which could now be evaluated with appropriate scale and rigor. On the other hand, the use of a surrogate outcome marker in the absence of a validated alternative, the inability to use either a biomarker or imaging to assess and corroborate clinical responses, the retrospective nature of the study/audit and lack of randomisation to treatment or placebo together with the dissimilarity of the study groups with regard to baseline BASDAI are important weaknesses with the capacity to bias outcomes. Nevertheless, we believe the indication of efficacy is strong and that future controlled studies are justified.

In summary, a substantial and mostly long-lasting response to TNFi therapy was observed in 8 of 12 patients with painful DISH (67% based on ITT analysis) treated empirically with TNFi for between 0.5 and 12.5y, compared to 1 of 7 (14%) untreated patients. These preliminary observations support TNFi efficacy in painful DISH and provide justification for a formal safety and efficacy study. It is acknowledged that without using a double blind randomised controlled trial design and a recruitment strategy with appropriate statistical power, it will be difficult to establish with confidence, the efficacy or otherwise of TNF inhibitors in the management of painful DISH. The audit reported here will help inform such power calculations and may stimulate further research in this disorder. The quality of future intervention studies in painful DISH might be significantly enhanced by the incorporation of serial MR imaging of the spine and SI joints.

Provenance: Internally reviewed
Ethical approval: Not required (see text)
Disclosures: None
Acknowledgement: We thank UCB Australia Pty Ltd for providing certolizumab for compassionate treatment of four patients, each for four months' duration. Fremantle Hospital Drug and Therapeutics Committee supported the use of TNFi drugs as an extension of therapy for selected patients offered compassionate supply.

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