Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: 2167-8421 (Print) 2167-9223 (Online) Journal homepage: http://www.tandfonline.com/loi/iafd20

"ALS reversals": demographics, disease characteristics, treatments, and co-morbidities

Daniel Harrison, Paul Mehta, Michael A. van Es, Elijah Stommel, Vivian E. Drory, Beatrice Nefussy, Leonard H. van den Berg, Jesse Crayle, Richard Bedlack & the Pooled Resource Open-Access ALS Clinical Trials Consortium

To cite this article: Daniel Harrison, Paul Mehta, Michael A. van Es, Elijah Stommel, Vivian E. Drory, Beatrice Nefussy, Leonard H. van den Berg, Jesse Crayle, Richard Bedlack & the Pooled Resource Open-Access ALS Clinical Trials Consortium (2018): "ALS reversals": demographics, disease characteristics, treatments, and co-morbidities, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, DOI: 10.1080/21678421.2018.1457059

To link to this article: https://doi.org/10.1080/21678421.2018.1457059

© 2018 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group

View supplementary material

Published online: 02 Apr 2018.

Submit your article to this journal

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
http://www.tandfonline.com/action/journalInformation?journalCode=iafd20

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2018; 1–5

Taylor & Francis
Taylor & Francis Group

Check for updates

RESEARCH ARTICLE

"ALS reversals": demographics, disease characteristics, treatments, and co-morbidities

DANIEL HARRISON[1], PAUL MEHTA[2], MICHAEL A. VAN ES[3], ELIJAH STOMMEL[4], VIVIAN E. DRORY[5], BEATRICE NEFUSSY[5], LEONARD H. VAN DEN BERG[3], JESSE CRAYLE[1], RICHARD BEDLACK[6] & THE POOLED RESOURCE OPEN-ACCESS ALS CLINICAL TRIALS CONSORTIUM‡

[1]School of Medicine, Duke University, Durham, NC, USA, [2]Agency for Toxic Substances and Disease Registry, National ALS Registry, Atlanta, GA, USA, [3]Department of Neurology, University Medical Center Utrecht, Utrecht, The Netherlands, [4]Department of Neurology, Geisel School of Medicine at Dartmouth, Hanover, NH, USA, [5]Department of Neurology, Tel-Aviv Medical Center, Tel-Aviv, Israel, and [6]Department of Neurology, Duke University and Durham VA Medical Center, Durham, NC, USA

Abstract

Objective: To identify differences in demographics, disease characteristics, treatments, and co-morbidities between patients with "amyotrophic lateral sclerosis (ALS) reversals" and those with typically progressive ALS. *Methods:* Cases of possible ALS reversals were found in prior publications, in the Duke ALS clinic, through self-referral or referral from other Neurologists, and on the internet. Of 89 possible reversals identified, 36 cases were included because chart or literature review confirmed their diagnosis and a robust, sustained improvement in at least one objective measure. Controls were participants in the Pooled Resource Open-Access ALS Clinical Trials database and the National ALS Registry. Cases and controls were compared using descriptive statistics. *Results*: ALS reversals were more likely to be male, have limb onset disease, and initially progress faster. The prevalences of myasthenia gravis (MG) and purely lower motor neuron disease in cases were higher than estimates of these prevalences in the general population. The odds of taking curcumin, luteolin, cannabidiol, azathioprine, copper, glutathione, vitamin D, and fish oil were greater for cases than controls. *Conclusions:* When compared to patients with typically progressive ALS, patients with reversals differed in their demographics, disease characteristics, and treatments. While some of these patients may have had a rare antibody-mediated ALS mimicker, such as atypical myasthenia gravis, details of their exams, EMGs and family histories argue that this was unlikely. Instead, our data suggest that ALS reversals warrant evaluation for mechanisms of disease resistance and that treatments associated with multiple ALS reversals deserve further study.

Keywords: *Amyotrophic lateral sclerosis*, *motor neuron disease*, *disease reversal*, *epidemiology*, *case control*

Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating and almost universally fatal neurodegenerative disease. Very rarely, a person who is diagnosed with ALS stops progressing and regains significant motor function. Studying these "ALS reversals" could uncover an under-recognized mimic syndrome, a genetic mechanism of ALS resistance, or possibly an effective treatment. Here, we compile verified cases of ALS reversals into a database to compare their demographics, disease characteristics, treatments, and co-morbidities to those of patients with more typically progressive ALS.

Methods

Data sources and study design

This was a case-control study. Potential cases were identified in prior peer-reviewed publications ($n = 23$), in the Duke ALS clinic ($n = 3$), through

‡Some data used in the preparation of this article were obtained from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database. As such, the following organizations and individuals within the PRO-ACT Consortium contributed to the design and implementation of the PRO-ACT Database and/or provided data, but did not participate in the analysis of the data or the writing of this report: Neurological Clinical Research Institute, MGH; Northeast ALS Consortium; Novartis; Prize4Life; Regeneron Pharmaceuticals, Inc.; Sanofi; Teva Pharmaceutical Industries, Ltd.

Correspondence: Daniel Harrison, Duke University, 932 Morreene Rd, Box 3333, Durham, NC 27705 United States. Tel: 832-483-5716. Fax 919-668-2901. E-mail: daniel.harrison@duke.edu

(Received 24 January 2018; revised 13 March 2018; accepted 18 March 2018)

ISSN 2167-8421 print/ISSN 2167-9223 online © 2018 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.
DOI: 10.1080/21678421.2018.1457059

self-referral or referral from other neurologists ($n = 40$), and from non-peer-reviewed anecdotes posted on the internet ($n = 23$). Patients in whom we could independently confirm an ALS or progressive muscular atrophy (PMA) diagnosis and a robust, sustained improvement in at least one objective measure through either chart or literature review ("ALS reversals") were included. Cases with ALS diagnoses met El Escorial-Revised and/or Awaji criteria (1,2). Reversals were most often measured by resolution of denervation on electromyogram (EMG), improved strength on manual muscle testing, and/or gains of at least 4 points on the ALS Functional Rating Scale-Revised (ALSFRS-R). In several instances, patients with only extraordinary improvements in activities of daily living were included. For example, we included one case who, at nadir, was unable to stand and after her improvement was able to walk several miles but did not have a formally documented strength exam. Patients with a relapse back to or below their previous nadir were excluded.

Details on the demographics, diagnoses, reversals, treatments, and co-morbidities of cases were compiled into a database. Controls ($n = 10{,}723$) were patients in the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database, downloaded 17 October 2016, volunteered by PRO-ACT Consortium members (Prize4Life, Northeast ALS Consortium, and ALS Therapy Alliance). Demographic and family history data from the online, self-enrolled portal of the National ALS Registry ($n = 6{,}352$) were also available for comparison.

Statistical analysis

Statistical analyses were conducted using JMP® Pro 13.0.0. Chi-squared analyses and two-sample *t*-tests were used to compare demographics and disease characteristics of cases to controls. Walk score progression was further evaluated with analysis of covariance. Wilcoxon's rank sum tests were used to compare age ranges. Treatments were compared using logistic regression with Bonferroni's correction.

Standard protocol approvals, registrations, and patient consents

This study was approved by the institutional review board of Duke University. There were no interventions and no protected health information was recorded during this study. Due to its very low risk, a waiver for informed consent was granted.

Results

Diagnoses and reversals

A total of 36 cases with clinically definite ALS ($n = 4$), clinically probable or clinically probable lab supported ALS ($n = 23$), clinically possible ALS ($n = 2$), and progressive muscular atrophy (PMA, $n = 7$) were confirmed through literature ($n = 16$) and chart review ($n = 20$). Information about their diagnoses and reversals is included in supplementary Tables 1 and 2. All had histories, neurological exams, EMGs and work up for mimics that made ALS more likely than not. Of note, 19% of cases had a purely lower motor neuron syndrome as compared to a population estimate of 5% of all patients with motor neuron disease (3). We considered these "progressive muscular atrophy" patients to have ALS for reasons outlined previously (4).

Following an initial decline, median time to maximum improvement was 12 months (range 1–206 months). There were 16 cases that were improving at their last known follow-up. Of 18 cases who plateaued after their maximum improvement, median duration of follow-up was 38.5 months (range 3–295 months). Length of follow-up could not be determined for two cases (participants 24 and 26) as their dates of maximum improvement were unavailable. Measures employed to track disease progression varied from case to case based on availability in the chart or original report. Potential cases with improvements on one or more objective measures were excluded if they showed deterioration on any other measures. There were 12 cases with improvements on the ALSFRS-R (mean 9.6, SD 4.7 points). The progression of ALSFRS-R scores from disease onset to last known follow-up are shown in Figure 1. In cases with improvements in strength on manual muscle testing, three or four limbs improved in the majority of cases. There were nine cases who regained normal strength and seven cases with full resolution of active denervation on EMG at the time of their reversals.

Demographics and disease characteristics

Comparisons between the demographics and disease characteristics of cases and controls are included in Table 1. Disease progression rate was measured by loss of points per year on ALSFRS-R walk score as few cases had fully documented ALSFRS-R scores at the time of their nadirs. After controlling for age and site of onset, walk score progression rate remained significantly faster for cases when compared to controls.

Co-morbidities

Neither PRO-ACT nor the National ALS Registry contains comprehensive information on the co-morbidities of their participants. However, the prevalence of a prior myasthenia gravis (MG) diagnosis in our cases (6%, $n = 2$, participants 34 and 35) was higher than estimates of prevalence in the general population (0.03%), though ALS and

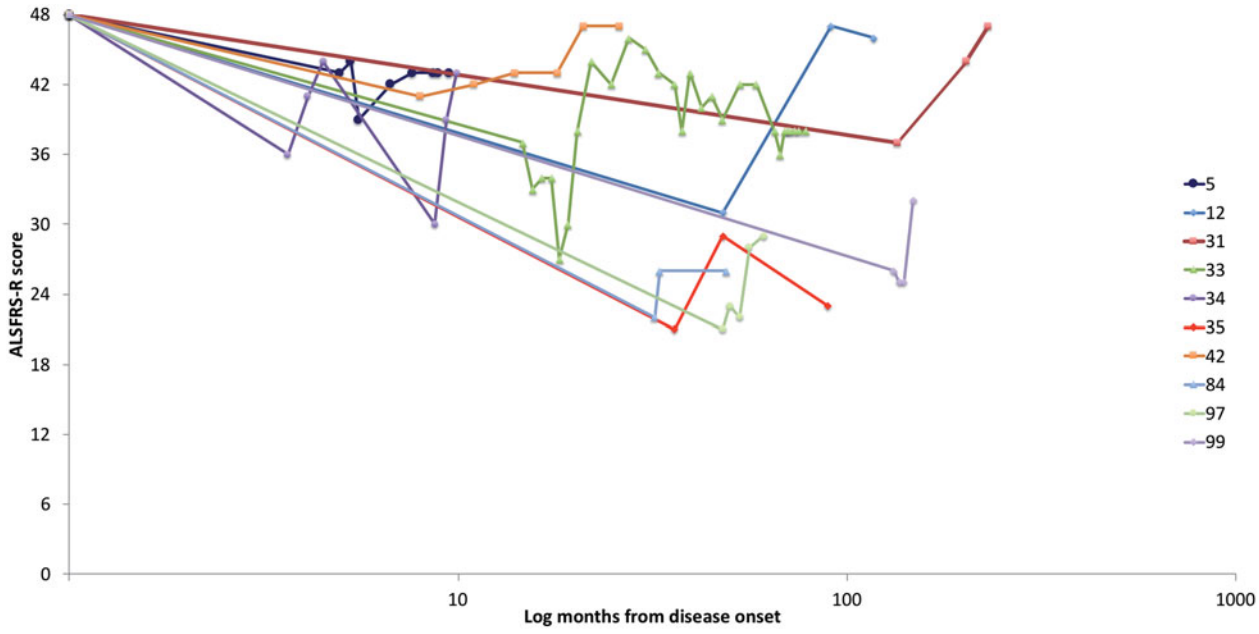

Figure 1. ALSFRS-R Progression. There were 12 cases with improvements measured by the ALSFRS-R. Of these, 10 are included in the figure (case 38 had initial measurements on the ALSFRS before the introduction of the ALSFRS-R and case 24 had an unknown date of maximum improvement). This chart shows the progression over time of these 10 cases as measured by the ALSFRS-R from disease onset to last known follow-up. Participants 5, 33, 34, 35, 42, and 99 had documented improvements on additional objective measures. ALSFRS(-R): amyotrophic lateral sclerosis functional rating scale(-revised).

Table 1. Demographics and disease characteristics of ALS reversals.

A	Cases	PRO-ACT	Statistical test	Result
Age of onset	50.1 (15.3)	53.8 (11.8)	$t=1.89$	$p=0.0588$
% Male	80.6	60.3	$\chi^2 = 6.14$	$p=0.0132$
% White	87.5	95.4	$\chi^2 = 3.36$	$p=0.0669$
% With family history of ALS	8.00	15.7	$\chi^2 = 1.10$	$p=0.2940$
% Limb onset	93.9	72.1	$\chi^2 = 7.80$	$p=0.0052$
Walk score progression rate	−1.59 (1.81)	−0.991 (0.762)	$t=4.28$	$p<0.0001$
B	**Cases**	**National ALS Registry**	**Statistical test**	**Result**
Age at diagnosis	50–59	50–59	$Z=2.88$	$p=0.0040$
% Male	80.6	60.5	$\chi^2 = 6.05$	$p=0.0139$
% White	87.5	95.2	$\chi^2 = 3.08$	$p=0.0792$
% With family history of ALS	4.00	4.20	$\chi^2 = 0.003$	$p=0.9594$

ALS: amyotrophic lateral sclerosis; ALSFRS-R: ALS Functional Rating Score–Revised; PRO-ACT: Pooled Resource Open-Access ALS Clinical Trials.

This table compares available demographics and disease characteristics of patients with ALS Reversals to patients in the PRO-ACT database (A) and the National ALS Registry (B). Family history data in the registry included first-degree relatives and family history data in PRO-ACT contained first-through third-degree relatives. As such, cases with first-through third-degree relatives with ALS were considered to have a family history in A and only cases with first-degree relatives with ALS were considered to have a family history in B. Only age ranges were available in the registry, which were compared using Wilcoxon's rank sum tests. Median age ranges were equivalent, however, rank sum of case age ranges was significantly less and rank sum of control age ranges was significantly greater than their expected values. Proportions were analyzed with Pearson's chi-square tests and means were analyzed with two-sample *t*-tests. Standard deviations are included in parentheses where applicable. Walk score progression rate is measured as change per year in points on the ALSFRS-R "walking" question.

MG may co-exist more frequently than predicted by chance alone (5).

Treatments

Supplementary table 3 includes information on treatments used by two or more cases at the time of their maximum improvement for which the odds of taking the treatment were significantly greater for cases than PRO-ACT controls. All of these treatments, with the exception of azathioprine, were used exclusively by cases identified through chart review. After controlling for age and site of onset, the odds of taking curcumin, azathioprine, copper, glutathione, vitamin D, and fish oil remained significantly greater for cases than controls. Insufficient data precluded this adjustment in patients who used luteolin or cannabidiol, but the odds of taking these two treatments remained

greater for cases than controls after controlling for age of onset.

Discussion

For the first time, we have compiled verified cases of ALS reversals into a database for comparison to patients with more typically progressive ALS. There are some differences in the demographics and disease characteristics of cases compared to controls. These differences persist across two groups of controls and are consistent with previously published data on ALS reversals (6). It is important to note that the definition of an ALS reversal used in this study differs from the previous definition, an improvement of four or more points on the ALSFRS-R lasting at least 12 months. Our new definition allows for the inclusion of patients with significant improvements who do not have documented ALSFRS-R scores. For example, one of our cases without an ALSFRS-R score came off a ventilator after 17 years of dependency and another began walking after a year of quadriplegia. Our new definition also requires that improvements be robust and sustained, as small, transient improvements in ALSFRS-R and muscle strength are not unusual in patients with typically progressive ALS (6,7). Concerns about previous work on ALS reversals from the PRO-ACT database included difficulty interpreting improvements on the ALSFRS-R without supporting data from other outcome measures and lack of information confirming work-ups for ALS mimic diseases. The majority of patients described here with improvements on the ALSFRS-R also had documented improvements on strength exam or other outcome measures. Additionally, all cases had available information regarding work-up for mimic diseases. While most patients had extensive imaging, EMG/nerve conduction studies, and laboratory work-ups, these varied widely from case to case.

One possible hypothesis is that some of our cases were misdiagnosed and may have had very rare antibody-mediated ALS mimic syndromes (8–14). The elevated rate of co-morbid MG and increased odds of azathioprine use in our cases may support this idea. Participant 34, for example, was diagnosed with seropositive MG with response to immunomodulation. He was diagnosed with ALS 2 years later after developing upgoing plantar reflexes, pseudobulbar affect, and brisk tendon reflexes in the arms and legs with signs of denervation and reinnervation on EMG in the absence of repetitive nerve stimulation decrement. Participant 35 was diagnosed with MG after a subacute episode of ptosis, dysarthria, dysphagia, and weakness that resolved fully within 2 months. He was diagnosed with PMA 30–40 years later based on widespread atrophy, weakness (greater distally in the upper extremities), and signs of denervation and reinnervation on EMG. However, MG and ALS may co-occur more often than expected by chance alone (5). The lack of fluctuating or ocular weakness, presence of upper motor neuron signs, and presence of EMG denervation in most of our cases make strong arguments that MG alone would not explain their presentations (15,16). The similar rate of ALS family history in our cases and controls argues further against the possibility that some of these cases were misdiagnosed.

The odds of taking curcumin, luteolin, cannabidiol, azathioprine, copper, glutathione, vitamin D, and fish oil were higher for cases than for controls. It is possible that a reporting or selection bias existed for cannabidiol in controls, as substance misuse would have excluded participants from at least some of the trials included in PRO-ACT. Associations do not prove causation. However, the eight therapies identified here are particularly interesting because they have plausible mechanisms by which they could influence ALS. For example, luteolin, glutathione, and vitamin D attenuate oxidative stress and fish oil, cannabidiol, and azathioprine reduce inflammation (17–22). Additionally, each therapy identified here was temporally associated with at least two reversals. These therapies should be further evaluated in prospective studies.

Finally, it is possible that our cases have genetic differences that confer disease resistance. There is a precedent for this in HIV elite controllers, and that discovery led to an effective treatment, maraviroc, for patients with HIV (23). One possibility is that some of these patients have mutations that lead to enhanced reinnervation. This might be of particular benefit in purely lower motor neuron disease, which was prevalent in our cases. We plan to perform whole genome sequencing on ALS reversals to determine if they differ genetically from patients with more typical ALS progression. By better understanding ALS reversals, we hope to make them happen more often.

Acknowledgements

The authors are grateful to all of the patients and families of patients living with ALS who shared their stories in hopes that they might help other PALS. Without their time and interest, this study would not have been possible. We also appreciate the assistance of Edwin Iversen, PhD and the Duke University Statistical Consulting Center for their statistical methods support. This work was supported by the LVH ALS Foundation [grant number 1].

Declaration of interest

Daniel Harrison, Paul Mehta, Elijah Stommel, Beatrice Nefussy, and Jesse Crayle report no

disclosures. Michael A van Es serves on the Motor Neurone Disease Association biomedical research advisory panel, has consulted for Biogen and has received travel grants from Baxalta and funding sources include the Netherlands Organization for Health Research and Development (Veni scheme), The Thierry Latran Foundation, the ALS Foundation Netherlands. Vivian Drory received research grants from the Israel Ministry of Science and Technology and Adelis Foundation. She is a paid consultant for Eyecontrol. Leonard H van den Berg has research grants from the Netherlands ALS Foundation. He serves on the Scientific Advisory Boards of Biogen, Cytokinetics and Orion. Richard Bedlack has research support from the ALS Association, the Motor Neurone Disease Association, Cytokinetics, Neuraltus, and GlaxoSmithKlein; he is a paid consultant for the ALS Association, Avanir, Cytokinetics, Neuraltus, Ultragenyx, Mallinkrodt and Brainstorm Cell.

ORCID

Daniel Harrison http://orcid.org/0000-0001-5381-9878

References

1. Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1:293–9.
2. Costa J, Swash M, de Carvalho M. Awaji criteria for the diagnosis of amyotrophic lateral sclerosis:a systematic review. Arch Neurol. 2012;69:1410–6.
3. Rowland LP. Progressive muscular atrophy and other lower motor neuron syndromes of adults. Muscle Nerve. 2010;41:161–5.
4. Kim WK, Liu X, Sandner J, Pasmantier M, Andrews J, Rowland LP, et al. Study of 962 patients indicates progressive muscular atrophy is a form of ALS. Neurology. 2009;73:1686–92.
5. de Pasqua S, Cavallieri F, D'Angelo R, Salvi F, Fini N, D'Alessandro R, et al. Amyotrophic lateral sclerosis and myasthenia gravis: association or chance occurrence? Neurol Sci. 2017;38:441–4
6. Bedlack RS, Vaughan T, Wicks P, Heywood J, Sinani E, Selsov R, et al. How common are ALS plateaus and reversals? Neurology. 2016;86:808–12.
7. Brooks BR. Natural history of ALS: symptoms, strength, pulmonary function, and disability. Neurology. 1996;47(4 Suppl 2):S71–S81; discussion S81-2.
8. Huijbers MG, Niks EH, Klooster R, de Visser M, Kuks JB, Veldink JH, et al. Myasthenia gravis with muscle specific kinase antibodies mimicking amyotrophic lateral sclerosis. Neuromuscul Disord. 2016;26:350–3.
9. Furuta N, Ishizawa K, Shibata M, Tsukagoshi S, Nagamine S, Makioka K, et al. Anti-MuSK antibody-positive myasthenia gravis mimicking amyotrophic lateral sclerosis. Intern Med. 2015;54:2497–501.
10. Basiri K, Ansari B, Okhovat AA. Life-threatening misdiagnosis of bulbar onset myasthenia gravis as a motor neuron disease: How much can one rely on exaggerated deep tendon reflexes. Adv Biomed Res. 2015;4:58.
11. Bedlack RSTS, Pastula DM. Reversible upper and lower motor neuron disease persisting long after infliximab therapy. In: PJ D, editor. Companion to peripheral neuropathy: illustrated cases and new development. 1st ed. Amsterdam, Netherlands: Elsevier Inc.; 2010.
12. Bersano E, Stecco A, D'Alfonso S, Corrado L, Sarnelli MF, Solara V, et al. Coeliac disease mimicking amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2015;16:277–9.
13. Ham H, Lee BI, Oh HJ, Park SH, Kim JS, Park JM, et al. A case of celiac disease with neurologic manifestations misdiagnosed as amyotrophic lateral sclerosis. Intest Res. 2017;15:540–2.
14. Turner MR, Chohan G, Quaghebeur G, Greenhall RC, Hadjivassiliou M, Talbot K. A case of celiac disease mimicking amyotrophic lateral sclerosis. Nat Clin Pract Neurol. 2007;3:581–4.
15. Petrou P, Argov A, Lennon VA, Gotkine M, Kassis I, Vaknin-Dembinsky A, et al. Rare combination of myasthenia and motor neuronopathy, responsive to Msc-Ntf stem cell therapy. Muscle Nerve. 2014;49:455–7.
16. ALSUntangled N. 26: lunasin. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15:622–6.
17. Pandey R, Mousawy K, Nagarkatti M, Nagarkatti P. Endocannabinoids and immune regulation. Pharmacol Res. 2009;60:85–92.
18. Wolfle U, Esser PR, Simon-Haarhaus B, Martin SF, Lademann J, Schempp CM. UVB-induced DNA damage, generation of reactive oxygen species, and inflammation are effectively attenuated by the flavonoid luteolin in vitro and in vivo. Free Radic Biol Med. 2011;50:1081–93.
19. Hayes JD, McLellan LI. Glutathione and glutathione-dependent enzymes represent a co-ordinately regulated defence against oxidative stress. Free Radic Res. 1999;31: 273–300.
20. Halicka HD, Zhao H, Li J, Traganos F, Studzinski GP, Darzynkiewicz Z. Attenuation of constitutive DNA damage signaling by 1,25-dihydroxyvitamin D3. Aging (Albany Ny). 2012;4:270–8.
21. Cleland LG, James MJ, Proudman SM. Fish oil: what the prescriber needs to know. Arthritis Res Ther. 2006;8:202.
22. Sahasranaman S, Howard D, Roy S. Clinical pharmacology and pharmacogenetics of thiopurines. Eur J Clin Pharmacol. 2008;64:753–67.
23. MacArthur RD, Novak RM. Reviews of anti-infective agents: maraviroc: the first of a new class of antiretroviral agents. Clin Infect Dis. 2008;47:236–41.

Supplementary material available online