RESEARCH

Low dose thiopurine and allopurinol co-therapy results in significant cost savings at a district general hospital

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Received 22 July 2014
Revised 17 October 2014
Accepted 18 October 2014
Published Online First 7 November 2014

ABSTRACT

Background Thiopurines are widely used for maintenance of remission in Crohn's disease (CD). Published data report >50% of patients stop thiopurines due to therapeutic failure, hepatitis or side effects. In this situation, many UK clinicians start biologics in CD patients. This has significant cost implications. An alternative strategy is low dose thiopurine and allopurinol (LDTA) co-therapy. We report the annual cost savings from adopting this strategy at our centre.

Methods Patients with CD treated with LDTA in preference to biological therapy were identified using a prospective local inflammatory bowel disease database. The annual drug cost of treatment with LDTA compared with biologic therapy was calculated. Cost of attending the day unit for an infusion was not included.

Results 26 patients with CD who failed standard dose thiopurine and were treated with LDTA were identified over a 12-month period and followed up for 1 year. 12 patients failed LDTA and progressed to biological therapy. The remaining 14 patients entered sustained clinical remission on LDTA. The cost savings achieved using the LDTA strategy in this group of patients was £146 413 per year with an average saving of £10 458 per patient per year.

Conclusions This study has identified a significant annual cost savings with this treatment strategy through the prevention of escalation to biologics. These cost savings are likely to be even more significant in the long term since a significant proportion of patients treated with biological therapy require dose escalation. We believe adopting this strategy more widely could lead to significant healthcare savings.

To cite: Dharmasiri S, Dewhurst H, Johnson H, *et al*. *Frontline Gastroenterology* 2015;**6**:285–289.

INTRODUCTION

Crohn's disease (CD) is a chronic incurable inflammatory condition of unknown aetiology that can result in significant symptoms. It is estimated that there are at least 120 000 patients with CD in the UK.[1] The majority of patients with CD require drug treatment and many will face surgery.[2] Buchanan *et al*[3] showed that a significant proportion of patients still required treatment 10 years after diagnosis and therefore incur ongoing healthcare costs. In the first health cost analysis of inflammatory bowel disease (IBD) since the introduction of biological therapy, Van der Valk *et al*[4] showed a shift in cost from principally being driven by hospitalisation and surgery[5] to medication cost, particularly anti-TNFα therapy. In fact, medication costs in their study accounted for 71% of healthcare cost associated with CD.

Spending on Healthcare in the UK is increasing at a faster rate than real gross domestic product (GDP). It is estimated that by 2070, healthcare spending will consume almost all of GDP if spending continues to grow at the same rate seen over the decade since 1999/2000.[6] This unsustainable growth in healthcare spending has led to pressure to cut costs while maintaining a high quality of patient care.

Thiopurines, azathioprine and mercaptopurine are well-accepted treatments for maintaining remission in IBD.[7–9] Therapeutic failure caused by poor response or adverse drug reactions (ADRs) occurs in up to 50% of patients.[10] The development of ADRs or treatment failure will usually necessitate cessation of thiopurine therapy.[11]

There is evidence linking the ADRs of azathioprine and mercaptopurine with methylated metabolites and that preferential methylation as well as high thiopurine

methyltransferase activity predicts biochemical hepatotoxicity.[12 13] Several studies from tertiary centres have demonstrated that low dose thiopurine (25%–33% of the usual dose) in combination with allopurinol[14] can avoid non-hepatitic ADRs,[15] is an effective treatment option in patients who have developed azathioprine induced biochemical hepatotoxicity[16 17] and improves disease outcome.[18–20] We have recently reported outcome data from a cohort of 62 patients with UC or CD that this therapy is both safe and effective in the district general hospital setting.[21]

In patients with CD, further treatment options include methotrexate, infliximab or adalimumab. ECCO guidelines suggest that methotrexate is contraindicated in both men and women who wish to conceive for 3–6 months prior to conception as well as throughout pregnancy thus limiting its use.[22] Furthermore, data suggest that to optimise efficacy it must be given parentally.[23 24]

In England and Wales, the National Institute of Health and Care Excellence (NICE) provide guidance on the cost effective use of medications within the National Health Service. The current NICE guidance advocates use of infliximab and adalimumab in patients with CD who have not responded to or are intolerant of conventional therapy (immunosuppressants and/or corticosteroids).[25]

Given that studies have shown that low dose thiopurine with allopurinol is safe, effective and can avoid ADRs, we hypothesised that this strategy will allow more patients to be successfully managed with thiopurines rather than escalated to more expensive treatment with biological agents and therefore confers a health cost benefit.

MATERIALS AND METHODS

We maintain a prospective database of all CD patients at our institution. It is our current practice to optimise use of thiopurines in patients who have developed ADRs by switching these patients to low dose thiopurine and allopurinol (LDTA) co-therapy, where this is safe (not thiopurine induced pancreatitis). We use thiopurine metabolite measurements to guide dosing. All patients with CD have a Harvey Bradshaw Index (HBI) calculated at each clinic visit to assess disease activity. Patients not responding to LDTA are escalated to biological therapy. We identified all patients over a 12-month period in which this strategy had been started and then analysed the cost savings in those where it prevented escalation to biological therapy for 12 months of follow-up. We performed cost of drug analysis on these patients based on the drug treatment they received over a year and also the cost per year should the patient have been escalated to biological therapy based on the weight of each individual patient. We used the unit costs published in the British National Formulary[26] together with those provided by our hospital pharmacy for our calculations; these are given in table 1. Smaller doses of azathioprine require the liquid formulation whereas for small doses of mercaptopurine capsules were used, the extra cost of which was factored into our analysis. In our local unit, current practice is to base the choice of biological drug on weight unless there is another indication for a particular drug. Patients who are 65 kg and over are treated with adalimumab whereas those under 65 kg are treated with infliximab to use the cheapest available drug in line with current NICE guidance.[25]

Table 1 Unit cost of drugs

Drug	Formulation	Cost (£)	Cost (€)
Azathioprine	150 mL of 50 mg/5 mL liquid	£97	€121.95
Mercaptopurine	10 mg capsules×50	£62.14	€77.95
Allopurinol	100 mg tablets×28	£0.28	€0.35
Infliximab	100 mg vial	£446.69	€561.63
Adalimumab	40 mg prefilled syringe (supplied by healthcare at home)	£352	€442.57

Patients started on adalimumab are given 160 mg at week 0, 80 mg at week 2 and then 40 mg every other week. Over a 12-month period, patients receive a total of 30×40 mg adalimumab injections. We use a standard infliximab induction regime of 5 mg/kg at weeks 0, 2 and 6 followed by 8 weekly 5 mg/kg infliximab; this equates to just under nine infusions per year. All infliximab infusions are given at the day unit within our hospital.

In our calculations, we have made the assumption that these patients would not have required anti-TNFα dose intensification. Therefore, our cost estimates for anti-TNFα therapy are the minimum cost per year of this therapy. In addition, we have not included the costs of attending the hospital day unit or drug administration costs associated with infliximab, which are significant.[27]

RESULTS

We identified 30 patients with CD over a 12-month period who had been started on LDTA following the development of ADRs. In all, 4 (13.3%) of these patients were already on biological therapy prior to instigation of LDTA and 12 (40%) patients progressed to biological therapy, the indications for which are given in table 2.

Drug cost analysis was performed on the remaining 14 (46.7%) patients. Baseline characteristics for the patients treated with LDTA and those escalated to biological therapy are given in table 3. There was no statistical difference in age, sex or Montreal Classification between the two groups.

The cost analysis results are summarised in tables 4 and 5. The combined cost savings achieved using the LDTA strategy in this group of patients was £146 412.57 per year with an average saving of £10 458.04 per patient per year.

Table 2 Indications for progression to anti-TNFα therapy

Age	M/F	Reason for stopping AZP/allopurinol
59	M	Intolerant of allopurinol taste
70	F	Nausea and vomiting
33	F	Disease progression
23	F	Disease progression
27	F	Disease progression
34	F	Pregnancy
36	M	Loss of appetite
66	F	Nausea and vomiting
85	M	Disease progression
35	F	Disease progression
60	M	Disease progression
28	F	Weight gain*

*Patient reported weight gain with LDTA and for this reason ceased LDTA and required escalation to anti-TNFα.
AZP, azathioprine; LDTA, low dose thiopurine and allopurinol.

Table 3 Montreal classification

Patients escalated to anti-TNFα therapy			Patients successfully treated LDTA for 1 year		
Age	M/F	Montreal classification	Age	M/F	Montreal classification
59	M	A3L2B1	66	M	A3L2B1
70	F	A3L2B1	55	F	A3L3B1
33	F	A2L3B1	39	F	A2L2B1
23	F	A2L3B3	48	M	A2L2B1
27	F	A2L3B1p	44	F	A2L3B2
34	F	A1L2B1	28	F	A2L3B1p
36	M	A2L1B3	65	F	A3L1B2
66	F	A3L3B1	43	M	A2L1B3
85	M	A2L3B3	49	M	A3L2B1
35	F	A2L3B3	60	M	A3L1B1
60	M	A3L2B1	35	F	A1L3B1
28	F	A2L1B2	72	M	A3L2B1
			66	M	A3L3B1
			67	M	A3L2B1

Sex, p=0.267 (Fisher's exact).
Montreal classification: A (p=0.609), L (p=0.879), B (p=0.609) (Fisher's exact).
Age, p=0.359 (Student's t test).
LDTA, low dose thiopurine and allopurinol.

DISCUSSION

Thiopurines have proven efficacy in the treatment of CD.[28 29] The major limiting factor for thiopurine therapy is the development of ADRs which usually results in its cessation.[30] In patients who are unable to tolerate thiopurines, accepted treatment strategies include starting an alternative immunosuppressant such as methotrexate with promising initial response rates but poor results in terms of sustained remission[31] or escalating to expensive biological therapy.[32] Another option is to use low dose thiopurine allopurinol co-therapy. This strategy allows a significant proportion of patients who have suffered with ADRs with thiopurines to continue with oral treatment. In the present study, we have demonstrated that by optimising the use of thiopurines a considerable drug cost saving is achieved. On average, in our unit, £10 458.44 per patient per year was saved. This is likely to underestimate the full cost savings achieved by the LDTA strategy since in our analysis we have only included the drug saving costs. In addition to a cost benefit, the LDTA strategy may have other benefits. Patients with IBD frequently experience social and psychological problems[33] and may easily become socially isolated.[34] The LDTA strategy allows patients to continue with oral medication avoiding the need to attend hospital for injections, which may alleviate some of the hospital attendance burden for the patient.

Several units have published data of their successful experience of LDTA in circumnavigating ADRs with thiopurines; to the best of our knowledge, this is the first study to report the cost savings achieved by the LDTA strategy.

Limitations of this study include the small number of patients included, its observational nature and that we have not compared disease outcome or quality of life in these patients with those escalated to treatment with biological therapy. However, it is unlikely that patients not escalated to biological therapy suffered worse clinical outcomes than those who were, as poor response to LDTA demonstrated by elevated/increasing HBI would have resulted in escalation to biological therapy according to our local practice. In the period covered by this study, all patients experiencing ADRs with thiopurines were switched to a LDTA strategy, reducing selection bias.

Table 4 Cost analysis for patients under 65 kg—infliximab

Sex	Age	Weight (kg)	Dose/ drug	TP monthly cost (£)	Allopurinol monthly cost (£)	Annual LDTA cost (£)	Infliximab dose cost (£)	Annual infliximab cost (£)	Annual drug saving (£)
F	55	54	35 mg/AZA	67.9	0.29	818.28	1340.07	12 060.63	11 242.35
F	39	53.5	25 mg/AZA	8.15	0.29	101.28	1340.07	12 060.63	11 959.35
F	28	56	25 mg/AZA	8.15	0.29	101.28	1340.07	12 060.63	11 959.35
								Total	35 161.05

AZA, azathioprine; LDTA, low dose thiopurine and allopurinol.

Table 5 Cost analysis for patients over 65 kg—adalimumab

Sex	Age	Weight (kg)	Dose/drug	Monthly cost (£)	Allopurinol monthly cost (£)	Annual LDTA cost (£)	Annual adalimumab cost (£)	Annual drug saving (£)
M	66	94	50 mg/AZA	3.76	0.29	48.60	10 560	10 511.40
M	48	78	50 mg/AZA	3.76	0.29	48.60	10 560	10 511.40
F	44	77	10 mg /MP	37.28	0.29	450.84	10 560	10 109.16
F	65	87	50 mg/AZA	3.76	0.29	48.60	10 560	10 511.40
M	43	65	40 mg/AZA	77.60	0.29	934.68	10 560	9625.32
M	49	90	20 mg/MP	74.57	0.29	898.32	10 560	9661.68
M	60	95	30 mg/MP	111.85	0.29	1345.68	10 560	9214.32
F	35	105	50 mg/AZA	3.76	0.29	48.60	10 560	10 511.40
M	72	74	25 mg/ AZA	8.15	0.29	101.28	10 560	10 458.72
M	66	78	40 mg/AZA	77.60	0.29	934.68	10 560	9625.32
M	67	104	50 mg/AZA	3.76	0.29	48.60	10 560	10 511.40
							Total	111 251.52

AZA, azathioprine; LDTA, low dose thiopurine and allopurinol; MP, mercaptopurine.

We recognise that a limitation of this study is that surgery, investigations and hospital visits were not included in our cost analysis. This study however reflects real-world clinical practice in our unit and we believe provides valuable data that the LDTA strategy in the setting of a district general hospital confers a significant drug cost saving. A larger multi-centre prospective trial is required to assess whether LDTA is a strategy that can cut overall healthcare cost associated with the management of CD.

Significance of this study

What is already known about this subject?

- Thiopurines are effective and widely used in the maintenance of remission of Crohn's disease.
- Therapeutic failure and adverse drug reactions lead to cessation of thiopurine therapy in up 50% of patients.
- The low dose thiopurine and allopurinol co-therapy strategy can be used to circumnavigate both hepatic and non-hepatic adverse drug reactions.

What are the new findings?

- Drug costs are higher in patients treated with biologic agents compared to thiopurines.
- Utilisation of the low dose thiopurine and allopurinol co-therapy strategy in patients with Crohn's disease previously intolerant of thiopurines confers a significant cost saving in the district general hospital setting.

How might it impact on clinical practice in the foreseeable future?

- These results suggest that the low dose thiopurine and allopurinol co-therapy strategy should be considered in patients with Crohn's disease previously intolerant of thiopurines to optimise health care resource.
- The significant cost savings that this strategy achieves could be used to further develop inflammatory bowel disease services in district general hospitals.

Contributors SD carried out data collection, data analysis and drafted the manuscript. HD performed data collection and data analysis. HJ performed data collection, data analysis and helped coordinate the study. SW performed data analysis, participated in coordination of the study and helped draft the manuscript. SM conceived the study, performed data analysis and helped draft the manuscript. All authors read and approved the final manuscript.

Competing interests SD—received financial support from Warner-Chilcott to attend the ECCO advanced IBD course and ECCO 9th Congress 2014. SW—has acted as an advisory board member for MSD and Abbvie. SM—has received honoraria and sponsorship to attend DDW conference from Abbvie.

Provenance and peer review Not commissioned; externally peer reviewed.

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