

Acetarsol in the management of mesalazine refractory ulcerative proctitis: A tertiary-level care experience.

Short Title: Acetarsol in refractory ulcerative proctitis

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Abstract

Background and Aims

Mesalazine-refractory ulcerative proctitis is common, with a significant proportion of the patients requiring escalation to immunomodulators or biological therapy. Three small preliminary cohort studies suggested good clinical efficacy for the organic arsenic derivative acetarsol in the management of proctitis. Our aim was to describe our experience on the use of acetarsol in proctitis and to review all existing evidence on its safety and efficacy.

Methods

We retrospectively reviewed clinical records of all ulcerative colitis patients exposed to acetarsol at Nottingham University Hospitals since 2012. Clinical response was determined basing on physicians' global assessments and patients' improvement over the baseline (reduction in stool frequency and rectal bleeding). Clinical remission was defined as total resolution of symptoms including bleeding cessation. Serum arsenic, C-reactive protein and fecal calprotectin levels reviewed when available. Non-parametric analysis performed.

Results

28 patients (16 males) with median (range) age 39 (35) and 9 (19) years disease duration received acetarsol suppositories for proctitis. All had failed mesalazine or corticosteroid topical therapy, with 50 % having additionally failed immunomodulators. Median treatment duration was 70 (64) days. 16/28 were prescribed acetarsol more than once. 67.9 % achieved clinical response and 46.4 % clinical remission. 32,1 % required treatment escalation to steroids, thiopurines or anti-TNF agents. 6/28 patients stopped acetarsol due to side effects.

Conclusions

Acetarsol could be an effective and safe option in the management of refractory proctitis. A definitive trial with long term safety follow-up is required to investigate the efficacy and safety of this promising drug.

Keywords: acetarsol, ulcerative proctitis, refractory proctitis, ulcerative colitis

Introduction

Ulcerative colitis (UC) is a chronic idiopathic inflammatory condition that affects the colonic mucosa in a continuous fashion. Disease extension in UC is classified as proctitis [E1], left-sided [E2] or extensive colitis [E3], with 31% of patients having proctitis at presentation. During follow-up, the disease will extend in 16 % of patients with proctitis, with the extent of colonic involvement having a major impact on treatment and long-term disease prognosis. (1)

Current European Crohn's and Colitis Organization guidelines suggest the use of topical mesalazine (5-ASA) preparations as first line treatment for proctitis, whilst its combination with oral 5-ASA or topical corticosteroids is reserved for patients with an inadequate response to topical 5-ASA. (2)

A lack of response to mesalazine occurs approximately in a quarter of the patients treated with mesalazine and requires treatment escalation to immunomodulators or biological agents. Recent cohort studies report success rates of 47% and 69% for azathioprine and infliximab respectively, whilst similar data from randomized controlled trials are unavailable, as disease limited to the rectum is usually an exclusion in such studies. Further options are needed to treat patients with refractory proctitis. (2-5)

Acetarsol is a pentavalent organic derivative of arsenic for which small preliminary studies suggested potential benefit in the management of refractory proctitis. (6-7)

Historically, acetarsol was effectively used in the management of protozoal infections, such as trichomoniasis, owing to its ability to form lethal arsenic bonds following its binding to protein-containing sulphhydryl groups that kill the parasite. (8) However, the anti-infective property of acetarsol do not explain its suggested efficacy in UC.

To date, several hypotheses have been proposed for the mode of action of acetarsol, possibly through its action on cellular energy pathways and DNA synthesis and repair; but, the exact mode of its action remains unknown. (9)

In the form of oral and intravenous preparations, the use of acetarsol has been associated with significant side effects (skin reactions, hematologic disorders, acrodynia and jaundice) and toxicity that significantly limited its use. (10-14) However, in the form

of rectal preparations, the preliminary reports from UC suggested far better tolerance. (6-7,15)

In our study, we describe our experience of the use of acetarsol suppositories in the management of ulcerative proctitis and we review all existing evidence on its safety and efficacy, highlighting issues and challenges for future studies.

Methodology

In November 2017, we retrospectively reviewed the electronic medical records of all of the adult patients who were prescribed acetarsol suppositories at the Nottingham University Hospital National Health Service Trust since 2012. Patients were identified through the hospital pharmacy database by the lead pharmacist. The Pharmacy Database comprised of drug dispensing records. These records included information regarding the type of drug, date of dispensing, strength, dosage regimen and route of administration and were coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System.

All dispensing records were reviewed by the authors and all patients were screened for eligibility. All eligible patients had histopathological confirmed ulcerative colitis, with most recent endoscopy showing disease confined to the rectum.

Patients with Crohn's disease, pouchitis, diversion colitis or active ulcerative colitis beyond the 20cm from the anus, were excluded.

Additional demographic and clinical data that were collected, included sex, age, date of histological diagnosis, disease location/Montreal Classification, inflammatory bowel disease (IBD)- related medication, repeated acetarsol prescriptions, clinical outcomes, endoscopic and safety reports. After the first administration of acetarsol, all patients' maintained medical records were prospectively reviewed until 11/2017 for occurrence of adverse events.

Clinical response was determined basing on physician's global assessment (PGA) and patients' symptomatic improvement over the baseline (reduction in stool frequency and bleeding reduction). Clinical remission was defined as total resolution of symptoms and

bleeding cessation in the absence of corticosteroid use or treatment escalation to immunosuppressants or biologics. (16)

Serum arsenic (nmol/l), serum C-reactive protein (CRP) (mg/dl) and fecal calprotectin levels were also reviewed if undertaken as part of standard of care.

The study was approved as a health care evaluation by Nottingham University Hospitals, Clinical Quality Risk and Safety Team:18-128h and conducted in accordance with the Helsinki Principles for the Protection of Patient Data.

Statistical Analysis

Due to the small sample size, the data were assumed to be non-parametric with relevant analyses undertaken. Continuous data are presented as median and range, while categorical variables are presented as frequencies.

The level of statistical significance was set for p values of less than 0.05. SPSS 17.0 statistical software for windows was used for the statistical analysis.

Results

Patient Demographics

From 01/2012 to 12/2015, 35 IBD patients were prescribed acetarsol suppositories and were screened for eligibility. One patient with diversion colitis, one with Crohn's disease, one with chronic pouchitis and four UC patients that were lost during follow up, were excluded from subsequent analysis. Figure 1 shows the flowchart of the study overview.

The final study cohort consisted of 28 UC patients (16 males; 12 females) with median (range) age of 39 (35) years. This included 24 patients who received acetarsol for ulcerative proctitis and 4 patients with more proximal disease who received acetarsol for residual proctitis. Population characteristics are shown in table 1.

All patients had previously failed treatment with topical or systemic 5-aminosalicylates and/or steroids with 14/28 (50%) having additional exposure to thiopurines and 2/28 (7.1 %) to oral ciclosporin.

The median (range) daily dose of acetarsol and treatment duration were 500 (500) mg and 70 days (64), respectively. 57.1 % of the population received more than one treatment prescription in an effort to maintain the clinical response or remission.

Clinical response was observed in 19 patients (67.9 %) and clinical remission in 46.4 %.

Endoscopy before and after treatment was performed in 3 patients, with 2 patients (66.7%) showing endoscopic improvement over the baseline.

After acetarsol discontinuation, 9 patients (32.1 %) needed treatment escalation [3 (10.7%) to corticosteroids, 4 (14.3 %), thiopurines and 2 (7.1 %) to anti-TNF agents].

During the treatment period, serum arsenic levels were available for 9/28 patients. Median (range) serum arsenic level was 777 (2776) nmol/l, (normal value < 130 nmol/l). Figure 2 shows an overall decrease in the serum arsenic levels of 6 patients with repeated measurements over time.

Serum CRP levels remained unchanged and within the normal range over the administration of acetarsol. No data identified for fecal calprotectin.

After the first administration of acetarsol, all patients were followed up for possible side effects. Median (range) follow up period was 6 (3) years. Over this period, 6/28 patients experienced possible acetarsol-related adverse events. [2 patients had headache, 1 vomiting, 1 perianal pruritus and paresthesia, 1 blepharitis and 1 sweating, palpitations and weakness]. All short-term side-effects ceased at treatment withdrawal. No malignancy or long-term complications had been reported.

Discussion

In our manuscript, we described our tertiary-level care experience on the use of acetarsol suppositories in a cohort of UC patients with mesalazine refractory proctitis.

In this refractory population, acetarsol was an effective therapy, with nearly half of the patients achieving clinical remission and two out of every three patients treated showing a clinical response. The therapeutic effect was temporary, with 57.1 % of our cohort requiring more than one prescription in an effort to preserve response or remission. The dose of acetarsol and the duration of treatment were determined exclusively by the treating physician, whilst the ongoing follow-up of each patient did not include the

routine monitoring of his/her serum arsenic levels. However, cross-sectional measurements of the serum arsenic levels were available for the one third of our population. Over the treatment period, a decreasing trend over time was observed for the arsenic levels, with the highest levels being recorded at the first weeks of treatment. The most likely reason for this observation is that acetarsol is highly absorbed through the friable mucosa, when the disease is active, but over time, its absorption rapidly drops, following the healing of the mucosa; nevertheless, detailed pharmacokinetic studies are needed to further investigate and validate our observations. After the first exposure to acetarsol, all of our patients' records were reviewed for short- and long-term adverse events for a median (range) period of 6(3) years. Over this period, no long-term adverse events were identified, but 6 out of the 28 patients experienced short-term gastrointestinal, cardiological and neurological side effects. All side effects ceased at medication withdrawal. In one case, the patient required admission due to severe headache and increased serum arsenic levels, with his/her overall status improving promptly with supportive measures.

To date, our knowledge on the use of acetarsol in the management of refractory UC proctitis is limited to two small studies. (6-7) Nearly three decades ago, Forbes et al. studied for the first time the efficacy of acetarsol suppositories in a cohort of UC patients with mesalazine refractory proctitis. In their open label trial, 10 patients received acetarsol suppositories 250mg twice daily for a period of 4 weeks, with their serum arsenic levels being prospectively monitored. Within 2 weeks, proctitis resolved clinically and endoscopically in 90% patients. Other than an excellent response to the acetarsol, this study showed that the arsenic is systematically absorbed by the inflamed intestinal mucosa, with the highest arsenic levels being recorded at the first week of treatment, similarly to our study. However, in 30% of the patients, the serum arsenic levels remained elevated after 4 weeks. The authors did not find any clinical consequence from this finding, but long-term therapy with acetarsol was not recommended. (7)

Recently, another cohort study from another center in the United Kingdom also looked at the efficacy of acetarsol in the management of proctitis. In this study, Kiely et al., by retrospectively reviewing the medical records of 39 IBD patients over a 6-year period, found that acetarsol was effective in 26 out of the 39 patients of their cohort, with one patient developing superficial dermatitis 1 week after commencing acetarsol, that

settled following the discontinuation of the drug. However, in this study, the case mix was heterogenous, as it additionally involved patients with refractory colonic Crohn's disease and hence, represents a different cohort to our patients. (6)

In our study, we included only UC patients with endoscopically confined disease to the rectum, who had previously failed treatment with mesalazine. However, a large proportion (57.1%) of our patients had also failed to thiopurines or ciclosporin. In this population, acetarsol was found to be well tolerated and of substantial benefit, but the response rate was less impressive than that observed by Forbes et al., with our findings indicating the increased refractory nature of our exposed cohort.

Based on these data, acetarsol might have a role in the treatment, not only of mesalazine refractory proctitis, but also of the residual rectal disease that's is resistant to treatment with immunosuppressive and biological agents.

Our study has limitation in particular its small cohort size and retrospective nature and hence, inability to collect data in a rigorous and homogenous fashion. Over the study period, no formal endoscopic or clinical disease activity scores were available. However, in the absence of more robust data, the utilization of PGA and of the rectal bleeding, which is the most sensitive UC symptom, in the evaluation of patients' clinical response or remission, gives credence to our results. (16-17)

In summary, our experience showed that acetarsol could be an effective and well tolerated option in the management of refractory proctitis. However, the evidence regarding its long-term efficacy and safety is limited. A definitive randomize controlled trial with long term safety follow-up is required to thoroughly investigate the efficacy and safety of this promising drug so as acetarsol to fill a niche in the UC pharmacotherapy.

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References

1. Burisch J, Ungaro R, Vind I, Prosberg MV, Bendtsen F, Colombel JF, et al. Proximal Disease Extension in Patients With Limited Ulcerative Colitis: A Danish Population-based Inception Cohort. *J Crohns Colitis*. 2017 Oct 1;11(10):1200-1204.
2. Harbord M, Eliakim R, Bettenworth D, Karmiris K, Katsanos K, Kopylov U, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. *J Crohns Colitis*. 2017 Jul 1;11(7):769-784.
3. Gecse KB, Lakatos PL. Ulcerative proctitis: an update on the pharmacotherapy and management: Expert Opin Pharmacother. 2014 Aug;15(11):1565-73.
4. Mallet AL, Bouguen G, Conroy G, Roblin X, Delobel JB, Bretagne JF, et al. Azathioprine for refractory ulcerative proctitis: A retrospective multicenter study. *Dig Liver Dis*. 2017 Mar;49(3):280-285.
5. Bouguen G, Roblin X, Bourreille A, Feier L, Filippi J, Nancey S, et al. Infliximab for refractory ulcerative proctitis. *Aliment Pharmacol Ther*. 2010 Jun;31(11):1178-85.
6. Kiely CJ, Clark A, Bhattacharyya J, Moran GW, Lee JC, Parkes M. Acetarsol Suppositories: Effective Treatment for Refractory Proctitis in a Cohort of Patients with Inflammatory Bowel Disease. *Dig Dis Sci*. 2018 Apr;63(4):1011-1015.
7. Forbes A, Britton TC, House IM, Gazzard BG. Safety and efficacy of acetarsol suppositories in unresponsive proctitis. *Aliment Pharmacol Ther*. 1989 Dec;3(6):553.
8. National Center for Biotechnology Information. PubChem Compound Database; CID=1985, <https://pubchem.ncbi.nlm.nih.gov/compound/1985> (accessed Apr. 29, 2018).
9. Hughes MF. Arsenic toxicity and potential mechanisms of action. *Toxicol Lett*. 2002 Jul 7;133(1):1-16.
10. Sasseville D, Carey WD, Singer MI. Generalized contact dermatitis from acetarsone. *Contact Dermatitis*. 1995 Dec;33(6):431-2.

11. Mohamed KN. Acetarsol-induced Stevens-Johnson syndrome. *DICP*. 1990 Jan;24(1):99-100.
12. Mukherjee BB, Ghose SK. Sudden blindness following injections of diethylamine acetarsol solution. *J Indian Med Assoc*. 1958 May 1;30(9):292-3.
13. Andre L, Marty J, Rispe R, Morichau-Beauchant J. Lymphoid leukemia in asyphilitic treated with sodium stovarsol and with bismuth. *Bull Mem Soc Med Hop Paris*. 1954 May 14-21;70(15-16):540-3.
14. Schrire V. Aplastic anaemia following therapeutic administration of stovarsol. *Clin Proc*. 1945;4(10):567-71.
15. Connell AM, Lennard-Jones JE, Misiewicz JJ, Baron JH, Jones FA. Comparison of acetarsol and prednisolone-21-phosphate suppositories in the treatment of idiopathic proctitis. *Lancet*. 1965; 1:238
16. Sandborn WJ, Sakuraba A, Wang A, Macaulay D, Reichmann W, et al. Comparison of real-world outcomes of adalimumab and infliximab for patients with ulcerative colitis in the United States. *Curr Med Res Opin*. 2016 Jul;32(7):1233-41.
17. D'Haens G, Sandborn WJ, Feagan BG, Geboes K, Hanauer SB, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology* 2007; 132: 763–86.