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Literature Scan: Inflammatory Bowel Agents (oral, rectal)

Date of Review: September 2015

Date of Last Review: May 2014
Literature Search: April 2014 – August 2015

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:

- There is low-quality evidence based on retrospective observational studies that 5-aminosalicylates (5-ASA) use may be associated with a reduced risk of colorectal cancer in patients with ulcerative colitis (Odds Ratio [OR] 0.63; 95% Confidence Interval [CI], 0.48 to 0.84).
- There is moderate-quality evidence 8 weeks of oral budesonide 9 mg daily is more effective than placebo for induction of remission of Crohn's disease (47% vs. 22%, respectively; Relative Risk [RR] 1.93; 95% CI, 1.37 to 2.73) but at the expense of more adverse effects.
- There is low quality evidence that budesonide is superior to placebo for short-term maintenance of remission of Crohn's disease (64% vs. 52%, respectively; RR 1.25; 95% CI, 1.00 to 1.58) but at the expense of more adverse effects. Longer-term remission rates (>3 months) do not differ between oral budesonide and placebo.
- There is moderate-quality evidence oral budesonide is less effective than traditional corticosteroids (ie, prednisone, prednisolone) for induction and maintenance of remission of Crohn's disease, but budesonide is associated with significantly fewer adverse effects.
- There is insufficient evidence to determine differences in efficacy or safety between budesonide and other oral agents for induction and maintenance of remission of Crohn's disease.
- There is low-quality evidence a rectal foam formulation of budesonide may induce remission in patient with mild to moderate distal ulcerative colitis compared to placebo based on 2 identical 6-week studies (response was 38.3% and 44.0% vs. 25.5% and 22.4%, respectively). However, most patients treated with budesonide did not respond to treatment with a 61.7% and 56.6% non-response rate in both studies).

Recommendations:

- No changes to current preferred 5-ASA products on the Oregon Health Plan (OHP) Preferred Drug List (PDL) are needed.
- Make oral budesonide, an oral corticosteroid formulation, available on the PDL for adjunctive management of mild Crohn's disease.
- Budesonide rectal foam should not be a preferred agent at this time due to limited short-term evidence.
- No further review of research needed at this time.

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Previous Conclusions:

- There is high quality evidence that 5-aminosalicylic acid is superior to placebo in inducing clinical remission (RR 0.86; 95% CI 0.81 to 0.91; NNT 9) and relapse (RR 0.69; 95% CI 0.62 to 0.77; NNT 5-8).
- There is moderate quality evidence of no difference between 5-aminosalicylate products and sulfasalazine in failure to induce clinical remission (RR 0.90; 95% CI 0.77 to 1.04) and high quality evidence of superiority of sulfasalazine in maintaining clinical remission (RR 1.14; 95% CI 1.03 to 1.27), with a higher rate or relapse associated with aminosalicylates.
- However, when including only the studies with outcomes at 12 months or taking the olsalazine trials out of the analysis, there was no difference between sulfasalazine and aminosalicylic acid in maintenance of clinical remission.
- There is moderate quality evidence of less withdrawals due to adverse events with oral 5-aminosaylciates compared to sulfasalazine (RR 0.40; 95% CI 0.24 to 0.69).
- There is moderate quality evidence of no difference between once daily dosing and conventional dosing in failure to induce clinical remission, maintaining clinical remission or adverse events and withdrawals due to adverse events.
- There is moderate quality evidence of no difference between different formulations of oral aminosayliclates in induction of clinical remission (RR 0.94; 95% CI 0.86 to 1.02) or adverse events and withdrawals due to adverse events (RR 0.94; 95% CI 0.57 to 1.54), and low quality evidence of no difference in maintaining clinical remission (RR 1.01; 95% CI 0.80 to 1.28).
- There is evidence that higher doses (≥ 3g/day) of aminosalicylate are more likely to induce clinical remission than lower doses.
- There is low quality evidence of no difference in maintenance of remission between rectal and oral formulations of 5-aminosalicylic acid (RR 1.24; 95% CI 0.92 to 1.66; p=0.15) for distal ulcerative colitis.

Previous Recommendations:

- Continue to maintain topical and oral options as preferred on the PDL.
- No further review of research needed at this time and review comparative costs to determine PDL placement of these agents.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2**. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

A systematic review[1] was conducted to identify and update the association between 5-ASA use in patients with ulcerative colitis and colorectal neoplasia (CRN), which included low- and high-grade dysplasia, and colorectal cancer (CRC). 5-ASA drugs approved in the U.S. for ulcerative colitis include balsalazide, mesalamine and sulfasalazine. All published studies that evaluated the effect of 5-ASA use on the risk of CRN were examined.[1] Seventeen studies (6 retrospective cohort studies and 11 case-control studies) containing 1,508 cases of CRN and 20,193 subjects published between 1994 and 2012 were analyzed.[1] Of the 1,508 cases of CRN, at least 75% of the cases were cases of CRC.[1] When data from all studies were pooled, 5-ASA use was associated with a reduced risk of CRC (OR 0.63; 95% CI, 0.48 to 0.84).[1] Reduction in CRN was primarily driven by case-control studies (OR 0.64; 95% CI, 0.45 to 0.90) because the retrospective cohort studies were underpowered to see a significant reduction (OR 0.59; 95% CI, 0.34 to 1.03).[1] However, significant heterogeneity between the studies was found (I^2=34.8%, p<0.001).[1] Different sensitivity analyses yielded non-significant reduction of CRN in the following: population-based studies (hospital-based studies showed a significant reduction); studies based in North America (European studies showed a significant protective benefit); patients with irritable bowel disease; and patients with extensive ulcerative colitis (proximal to splenic flexure).[1] Studies that evaluated a higher average daily dose of 5-ASA (sulfasalazine ≥2 g/day, mesalamine ≥1.2 g/day) found a lower associated risk of CRN (OR 0.51; 95% CI, 0.35 to 0.75).[1]

A Cochrane Review[2] evaluated the efficacy and safety of oral budesonide for induction of remission in Crohn's disease. Induction of remission was defined as Crohn's Disease Activity Index [CDAI] <150 or Pediatric Crohn's Disease Activity Index [PCDAI] <10 by 8-16 weeks of therapy.[2] Randomized controlled trials that compared budesonide to a control (active or placebo) were evaluated.[2] Fourteen studies (n=1805) were included in the review: 3 studies compared budesonide to placebo; 9 studies compared budesonide to traditional corticosteroids; and 2 studies compared budesonide to mesalamine.[2] Moderate quality evidence showed that budesonide 9 mg daily was significantly more effective than placebo after 8 weeks for reduction of clinical remission (47% vs. 22%, respectively; Relative Risk [RR] 1.93; 95% CI, 1.37 to 2.73; I^2=0%).[2] However, moderate quality evidence showed budesonide was significantly inferior to traditional corticosteroids (ie, prednisone, prednisolone, etc.) for reduction of clinical remission at 8 weeks (61% vs. 52%, respectively; RR 0.85; 95% CI, 0.75 to 0.97; I^2=0%), though risk of bias was judged to be high with these studies.[2] There was significant heterogeneity between the 2 studies that compared budesonide to mesalamine (I^2=81%) so data were not pooled.[2] Both studies had conflicting results: 1 study demonstrated significant superiority for budesonide 9 mg daily for reduction of remission at 8 weeks compared to mesalamine 4 g daily (RR 1.63; 95% CI, 1.23 to 2.16) but another study did not a difference between these interventions at 8 weeks (RR 1.12; 95% CI, 0.95 to 1.32), though a significant benefit was observed at 12 and 16 weeks.[2] Budesonide was similarly tolerated as mesalamine, but budesonide was better tolerated than traditional corticosteroids with fewer reported adverse events (RR 0.64; 95% CI, 0.54 to 0.76).[2] In addition, abnormal adrenocortical stimulation tests (ACTH) were significantly lower with budesonide than with traditional corticosteroids (RR 0.65; 95% CI, 0.55 to 0.78).[2]

A Cochrane Review[3] evaluated the efficacy and safety of oral budesonide for maintenance of remission (CDAI ≤150) following initiation of maintenance therapy in Crohn's disease. Randomized controlled trials that compared budesonide to a control (active or placebo), or that compared 2 doses of budesonide, were evaluated.[3] Twelve studies (n=1273) were included in the review: 8 studies compared budesonide to placebo; 1 study compared budesonide to 5-ASA, 1 study compared budesonide to traditional corticosteroids, 1 study compared budesonide to azathioprine, and 1 study compared 2 different doses of budesonide.[3] Budesonide 6 mg daily was not more effective than placebo for maintenance of remission at 3 months or anytime thereafter.[3] Low quality evidence showed at 3 months 64% of budesonide treated patients remained in remission compared to 52% of placebo patients (RR 1.25; 95% CI, 1.00 to 1.58).[3] The quality of evidence was judged to be low due to moderate heterogeneity (I^2=56%) and the limited amount of overall events.[3] At 6 months, moderate quality evidence showed 61% of budesonide treated patients remained in remission compared to 52% of placebo patients (RR 1.15; 95% CI, 0.95 to 1.39) but the quality of evidence was limited by the small number of events.[3] The results at 12 months between budesonide treated patients and placebo were similar to results observed at 6 months (RR 1.13; 95% CI, 0.94 to 1.35).[3] Current recommended dosing of oral budesonide for maintenance of remission is congruent with the evidence demonstrated in

these studies: “continued treatment beyond 3 months has not demonstrated to result in substantial benefit”.[4] Low quality evidence (due to limited data from one study) showed there was no significant difference in continued remission at 3, 6, or 12 months between budesonide 9 mg daily and prednisolone 40 mg daily with a weaning schedule (50% vs. 64%, respectively; RR 0.79; 95%CI 0.55 to 1.13).[3] Very low quality evidence suggested budesonide 6 mg daily was superior to mesalamine 3 g daily when remission rates were assessed at 12 months (45% vs. 18%, respectively; RR 2.51; 95% CI, 1.03 to 6.12), but this was based on one small, open-labeled study.[3] Very low quality evidence also suggested budesonide was equal to azathioprine at 12 months (64% vs. 79%, respectively; RR 0.81; 95% CI 0.61 to 1.08) based on 1 small, single-blinded study without appropriate concealment of allocation.[3] The number of adverse drug events was similar in patients treated with budesonide compared to placebo (RR 1.51; 95% CI 0.90 to 2.52) and did not result in increased rates of study withdrawal.[3] The more commonly reported events were similar to those seen with systemic corticosteroids and included acne, moon facies, hirsutism, mood swings, insomnia, weight gain, striae, and hair loss.[3] Abnormal ACTH tests were more frequently observed in patients who received budesonide 6 mg daily (RR 2.88; 95% CI, 1.72 to 4.82) compared to placebo.[3]

New Guidelines:
None identified.

New FDA Drug Approvals:
None identified.

New Formulations/Indications:
Uceris (budesonide) 2 mg rectal foam was approved in October 2014 to induce remission in patients with active mild to moderate distal ulcerative colitis (ie, ulcerative proctitis [UP] or ulcerative protcosigmoiditis) extending up to 40 cm from the anal verge.[5] Budesonide 2 mg rectal foam has topical anti-inflammatory properties, weak mineralocorticoid activity and undergoes significant first-pass elimination.[6] These properties result in limited systemic bioavailability, which theoretically reduce systemic adverse effects commonly observed with traditional corticosteroids.[6] This particular formulation is an emulsion provided in an aluminum container with an aerosol propellant.[6]

BACKGROUND: In contrast to more extensive ulcerative colitis, UP typically follows a more benign course with less severe symptoms but will often extend proximally and eventually involve more medication.[6] Topical medication with rectally administered 5-ASA and corticosteroid suppositories or enemas are effective treatment for most patients with UP.[6] The combination of topical 5-ASA and oral 5-ASA or topical steroids is considered when escalation of treatment is required.[6] Patients refractory or intolerant to 5-ASAs and corticosteroids may eventually require immunomodulators or biological therapy.[6]

EFFICACY/SAFETY: There were 2 replicate 6-week, phase 3, multi-centered, randomized, double-blind, placebo-controlled trials (BUCF 3001 and BUCF 3002) designed to assess the efficacy of budesonide 2 mg rectal foam (dosed twice daily for 2 weeks, followed by once daily for 4 weeks) in patients with mild to moderate distal ulcerative colitis.[6] Patients included in the trials had baseline Modified Mayo Disease Activity Index (MMDAI) scores of 5 through 10 with a score of ≥2 on the MMDAI rectal bleeding component and ≥2 on the MMDAI endoscopy or sigmoidoscopy component.[6] The primary outcome was the proportion of patients who achieved remission at the end of 6 weeks.[6] Remission was defined as components of an endoscopy score of ≤ 1, a rectal bleeding score of 0, and an improvement or no change from baseline in stool frequency sub-scales of the MMDAI at the end of 6 weeks of treatment or withdrawal.[6] Baseline characteristics were similar between the groups in both studies (ie, extent of disease, stools per day, duration of disease).[6] Over half of the patients studied were concomitantly on oral 5-ASA. Remission rates for the 2 studies are described in Table 1.[6]

Table 1. Remission Rates After 6 Weeks of Budesonide Rectal Foam or Placebo (Studies BUCF 3001 and BUCF 3002).[6]

	Study BUCF 3001			Study BUCF 3002		
Efficacy Endpoint	Budesonide Foam (n=133)	Placebo (n=132)	p-value	Budesonide Foam (n=134)	Placebo (n=147)	p-value
Achieved Remission						
Responder	51 (38.3%)	34 (25.8%)	p=0.03	59 (44.0%)	33 (22.4%)	p<0.001
Non-Responder	82 (61.7%)	98 (74.2%)		75 (56.0%)	114 (77.6%)	

Results demonstrate a significant difference between budesonide foam and placebo at induction of remission; however, there were also a very large number of non-responders.[6] There was also a trend towards higher remission rates that correlated with greater extent of disease activity – higher baseline MMDAI scores were associated with greater response with budesonide rectal foam.[6]

The safety profile of budesonide rectal foam is similar to that observed with the oral formulation of Uceris (budesonide).[6]

New FDA Safety Alerts:
None identified.

References:

1. Zhao L, Li J, Yu T, Chen G, Yuan Y, Chen Q. 5-aminosalicylates reduce the risk of colorectal neoplasia in patients with ulcerative colitis: an updated meta-analysis. *PLoS ONE*. 9(4):e94208. doi:10.1371/journal.pone.0094208.

2. Rezaie A, Kuenzig M, Benchimol E, et al. Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2015;6:Art. No. CD000296. doi:10.1002/14651858.CD000296.pub4.

3. Kuenzig M, Rezaie A, Seow C, et al. Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2014;8:Art. No. CD002913. doi:10.1002/14651858.CD002913.pub3.

4. ENTOCORT EC (budesonide) [prescribing information]. Sodertalje, Sweden: AstraZeneca AB, December 2011.

5. UCERIS (budesonide) [prescribing information]. Raleigh, NC: Salix Pharmaceuticals, Inc., October 2014.

6. Uceris (budesonide) Rectal Foam 2 mg Summary Review. Application No: 205613Orig1s000. Center for Drug Evaluation and Research, Food and Drug Administration. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205613Orig1s000SumR.pdf. Accessed 5 August 2015.

Author: Andrew Gibler, Pharm.D. Date: September 2015

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRANDE NAME	GENERIC NAME	PDL
ORAL	CAP ER 24H	APRISO	MESALAMINE	Y
ORAL	CAPSULE	BALSALAZIDE DISODIUM	BALSALAZIDE DISODIUM	Y
ORAL	CAPSULE	COLAZAL	BALSALAZIDE DISODIUM	Y
ORAL	CAPSULE	DIPENTUM	OLSALAZINE SODIUM	Y
ORAL	TABLET	AZULFIDINE	SULFASALAZINE	Y
ORAL	TABLET	SULFASALAZINE	SULFASALAZINE	Y
ORAL	TABLET	SULFAZINE	SULFASALAZINE	Y
ORAL	TABLET DR	ASACOL	MESALAMINE	Y
ORAL	TABLET DR	AZULFIDINE	SULFASALAZINE	Y
ORAL	TABLET DR	LIALDA	MESALAMINE	Y
ORAL	TABLET DR	SULFASALAZINE	SULFASALAZINE	Y
ORAL	TABLET DR	SULFASALAZINE DR	SULFASALAZINE	Y
ORAL	TABLET DR	SULFAZINE EC	SULFASALAZINE	Y
RECTAL	SUPP.RECT	CANASA	MESALAMINE	Y
ORAL	CAPSULE DR	DELZICOL	MESALAMINE	N
ORAL	CAPSULE ER	PENTASA	MESALAMINE	N
ORAL	TABDR & ER	UCERIS	BUDESONIDE	N
ORAL	TABLET	GIAZO	BALSALAZIDE DISODIUM	N
ORAL	TABLET DR	ASACOL HD	MESALAMINE	N
RECTAL	ENEMA	MESALAMINE	MESALAMINE	N
RECTAL	ENEMA	SFROWASA	MESALAMINE	N
RECTAL	ENEMA KIT	MESALAMINE	MESALAMINE W/CLEANSING WIPES	N
RECTAL	ENEMA KIT	ROWASA	MESALAMINE W/CLEANSING WIPES	N
RECTAL	FOAM/APPL	UCERIS	BUDESONIDE	N
ORAL	CAPDR - ER	BUDESONIDE EC	BUDESONIDE	
ORAL	CAPDR - ER	ENTOCORT EC	BUDESONIDE	

Appendix 2: New Clinical Trials

No relevant comparative clinical trials published since April 2014 were identified for this literature scan.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 4 2015

1 exp Colitis, Ulcerative/ 13899
2 balsalazide.mp. 102
3 exp Mesalamine/ 2084
4 exp Sulfasalazine/ 1563
5 exp Budesonide/ 3063
6 2 or 3 or 4 or 5 6432
7 1 and 6 1134
8 limit 7 to (yr="2014 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 16

Ovid MEDLINE(R) without Revisions 1996 to July Week 4 2015
1 exp Budesonide/ 3063
2 exp Crohn Disease/ 18412
3 1 and 2 190
4 limit 3 to (yr="2014 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 2