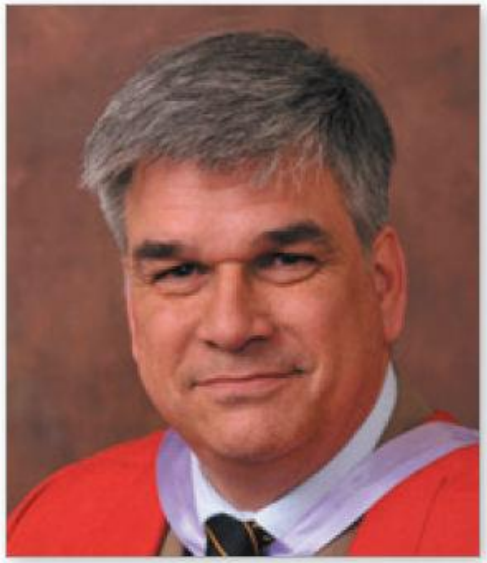

Professor Michael Schultz

Professor

Gastroenterologist and

Head of Department Dunedin School of Medicine

Sunday, August 11, 2019

(Room 10)

8:30 - 9:25 WS #154: Case Studies in Gastroenterology

9:35 - 10:30 WS #164: Case Studies in Gastroenterology (Repeated)

Therapeutic drug monitoring

Dr Sethu Nagappan

Gastroenterology Registrar

Dunedin Hospital

Case

- Miss Ab
- 24 year old
- She developed watery diarrhoea associated with blood, increasing frequency, urgency, and crampy abdominal pain in December 2014
- Rigid sigmoidoscopy was performed and this showed proctitis.
- She was commenced on Pentasa 1.5 gram bd

Case

- Miss Ab then developed further flare of symptoms including watery diarrhea and PR bleeding with elevated CRP
- Colonoscopy was then done which showed diffuse inflammation throughout the colon consistent with pancolitis secondary to Ulcerative Colitis
- Biopsies taken throughout the colon showed inflammatory infiltrate in all samples from caecum distally
- She was commenced on steroids
- Referred to Gastroenterology outpatient clinic in Dunedin Hospital in June 2015

Case

- Seen in clinic in June 2015
- By this time, her symptoms had largely responded to prednisone
- On tapering down dose of prednisone
- She was passing 1 to 2 bowel motions/day with only intermittent blood seen
- Her pentasa was increased to 2 gram bd
- Plan was to add Azathioprine

TPMT

- Her TPMT (Thiopurine Methyltransferase level) was elevated at 21.6 units/ml RBC (Range 9.3 to 17.6)
- In view of high TPMT activity, it was felt higher than usual dose could be considered on her
- Her weight was 79 kg
- She was commenced on Azathioprine 50 mg daily with plan to increase to 100 mg daily and 150 mg daily within weeks
- Aiming for 2 mg/kg dose of Azathioprine

Progress

- Miss Ab went into remission
- She was on Pentasa 1.5 gram bd and Azathiporine at 150 mg od
- Had Azathioprine metabolites checked in August 2015
- Elevated 6 TGN level of **1405** pmol/8 x 10(8) RBC's
- Elevated 6 MMP level of **4460** pmol/8 x 10(8) RBC's
- 6 TGN therapeutic ranges for IBD is 235-450 pmol/8 x 10(8) RBC's. Significant Leukopenia is more likely at level more than 450
- 6 MMP concentrations above 5700 is associated with hepatotoxicity
- Despite the elevated levels, she did not report any side effects
- Normal FBC and LFT's

Dose reduced

- Her Azathioprine dose was reduced from 150 mg daily to 100 mg daily
- Unfortunately during this time, she developed crampy abdominal pain with a gradual increase in stool frequency and with blood in about 50% of the motions.
- Rigid sigmoidoscopy showed there was patchy inflamed mucosa with erythema, contact bleeding and some ulceration at 20cms with normal looking mucosa in between. Biopsies taken showed chronic active colitis with ulceration
- Patient was commenced on course of steroids for flare

Azathioprine metabolite levels

- Repeat testing in October 2015 showed elevated 6 TGN level of **628** pmol/8 x 10(8) RBC's , MMP level of **478** pmol/8 x 10(8) RBC's
- Levels still elevated, patient advised to reduce dose of Azathioprine from 100 mg daily to 75 mg daily.
- Patient weaned off Steroids
- Remained well while on Azathioprine 75 mg daily and Pentasa 1.5 gram bd
- Repeat testing in February 2016 showed elevated 6 TGN level of **741** pmol/8 x 10(8) RBC's , MMP level of **289** pmol/8 x 10(8) RBC's
- Azathioprine dose reduced from 75 mg daily to 50 mg daily

Progress

- In April 2016, patient started developing symptoms of flare again
- Colonoscopy repeated in May 2016 showed extensive pan colonic ulcerative colitis
- Assessed for clinical trial but did not meet inclusion criteria for trial due to low Hb
- Commenced on further course of steroids in August 2016, came off this in Nov 2016
- Repeat testing in August 2016 showed 6 TGN level of **569** pmol/8 x 10(8) RBC's and in September 2016 showed 6 TGN level of **279** pmol/8 x 10(8) RBC's
- Patient remained on Aza dose of 50mg daily

Infliximab

- Infliximab started in December 2016
- Induction dose at week 0, 2 and 6 followed by 8 weekly infusions
- She responded well and her symptoms improved
- She continued on Azathioprine 50 mg daily and infliximab 8 weekly infusions
- Azathioprine metabolites testing in March 2017 showed 6 TGN level of **275** pmol/8 x 10(8) RBC's and in September 2017 showed 6 TGN level of **150** pmol/8 x 10(8) RBC's

Infliximab levels

- Patient remained well and her symptoms were well controlled at this stage
- She then developed flare of colitis symptoms again in February 2018.
- Needed course of steroids
- Infliximab levels and ant-infliximab antibodies were checked for in February 2018
- Infliximab level was low at 0.2 mg/L
- Anti-infliximab antibodies were not detected

Increase dose of infliximab

- Decision made that patient able to continue on infliximab
- As no antibodies against infliximab was detected
- Flare could be due to secondary loss of response to infliximab
- As infliximab levels were low, her infliximab dose was increased to 10mg/kg body weight from 5 mg/kg body weight for next 3 days to recapture control
- Control and remission was able to be re-captured and patient was well again
- In August 2018, infliximab level was 15.3 mg/L
- Patient then went back on Infliximab 5 mg/kg body weight and remained on Azathioprine 50 mg/day

Good progress

- Since then, patient has been doing well
- Seen in clinic this month, her inflammatory markers are normal
- Continuing on 8 weekly Infliximab 5 mg/kg body weight and Azathioprine 50 mg daily

Summary

- Mrs Ab was commenced on Azathioprine in June 2015
- Had azathioprine metabolite levels checked in August 2015, with reduction in Azathioprine dose from 150 mg daily to 100 mg daily
- Repeat metabolite testing done in October 2015, February 2016 with subsequent reduction in dose to 75 mg and 50 mg respectively
- Patient maintained on stable dose of 50 mg daily and had metabolite testing done in August and September 2016 when she developed flare of symptoms
- This showed she had good 6 TGN levels so Azathioprine dose maintained
- She had 1 flare while initially on Pentasa and she had 3 flares while on Azathioprine requiring steroids

Summary

- Commenced on Infliximab in December 2016
- Following 14 months on Infliximab, she developed flare of symptoms in February 2018
- Infliximab level was found to be low but anti-infliximab antibodies were not detected
- Infliximab dose was increased for next 3 doses and control of symptoms was able to be re-captured
- Remained well since on regular Infliximab infusions and Azathioprine combination