Concurrent cytomegalovirus (CMV) infection in inflammatory bowel disease (IBD) related colitis, (Ulcerative Colitis [UC] or Crohn’s Disease [CD]) is an important yet complex scenario associated with high rates of colectomy and other morbidity.

This regional audit aimed to identify baseline standards for a diagnostic virological-based approach for the identification of those at risk of CMV reactivation (flare) in the setting of IBD. CMV is a member of the Herpesvirus family and transmission (typically respiratory) in the vast majority of healthy individuals usually results in asymptomatic infection and establishes latency; the seroprevalence of CMV in the adult population is between 70-100%.

Clinically significant CMV disease is almost universally seen in the immunocompromised, including those with IBD. Principle reservoirs of CMV leading to reactivation are the myeloid and endothelial cell populations. As vascular endothelium is the interface between circulating immune cells and the lamina propria of the gut, this helps explain the role of CMV in IBD. CMV replication is usually the result of reactivation rather than primary infection.

This audit is a regional study of laboratory investigation of CMV colitis, to establish current protocol in line with clinical guidelines. The Gold Standard diagnostic approach to CMV associated colitis is Histological H&E, and IHC with the classic ‘owl’s eye appearance’ of CMV inclusion bodies. The Regional Virus Laboratory (RVL), investigates CMV via either serology assays (antibody assay/ELISA) or molecular (Quantitative PCR). Specimen types typically received for investigation of CMV in IBD are serum (edema), faeces, or tissue (sigmoidoscopy biopsy). This audit aims to look at the specimen types received and interpretation of results clinically for a cohort of IBD patients, in line with histopathology findings; and so help determine a local protocol as a diagnostic algorithm. This audit also attempts to look at management in terms of use of antivirals, the laboratory turn-around times (result communication), and colectomy rates, in this cohort of patients.

Aims

‘To improve the detection and management of CMV colitis in patients with IBD’

Material and Methods

- Retrospective, cross-sectional study over a three year time period, January 2010 - March 2013. Involving all Northern Ireland Health and Social Care Trusts (HSCs);
- Belfast HSC, Western HSC, Southern HSC, South Eastern HSC, and Northern HSC;
- A total of 9 IBD nurse grade staff* collated data to a Microsoft Access proforma for assessment. Data included patient demographics/histopathology clinical data/clinical data investigations’ clinical course and laboratory results
- Sample cohort: n=277 IBD patients of which n=106 further grouped as SAC/SRC ‘severe acute colitis and/or steroid refractory colitis’;
- Six audit standards were assessed including specimen(s) submission for CMV diagnostic laboratory analysis, antiviral therapy, ascertainment of colectomy, and result communication protocol as in table 1

Audit Standards

1. During admission (SAC/SRC) patients to have colonic biopsy tissue submitted for histopathology
2. During admission (SAC/SRC) patients to have colonic biopsy tissue submitted for Cytology
3. Establish baseline for specimen submission of blood and faeces for CMV virological investigation (serology and PCR)
4. Upon confirmation of CMV colitis via a combination of colonic histology and/or PCR patients should be treated with antiviral agents
5. Establish a protocol for rapid communication of virology results is in place
6. Establish a baseline of surgical intervention in the form of colectomy in CMV positive IBD patients

Table 1: Audit Standards

<table>
<thead>
<tr>
<th>Standard</th>
<th>Audit Details</th>
<th>Target</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>During admission (SAC/SRC) patients to have colonic biopsy tissue submitted for histopathology</td>
<td>100%</td>
<td>100% (all which CMV positive IBD positive)</td>
</tr>
<tr>
<td>2</td>
<td>During admission (SAC/SRC) patients to have colonic biopsy tissue submitted for Cytology</td>
<td>100%</td>
<td>100% (all which CMV positive IBD positive)</td>
</tr>
<tr>
<td>3</td>
<td>Establish baseline for specimen submission of blood and faeces for CMV virological investigations</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td>Upon confirmation of CMV colitis via a combination of colonic histology and/or PCR patients should be treated with antiviral agents</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>5</td>
<td>Establish a protocol for rapid communication of virology results is in place</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>6</td>
<td>Establish a baseline of surgical intervention in the form of colectomy in CMV positive IBD patients</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Results

- SAC/SRC patients are at a higher risk of colectomy than the non-SAC/SRC patients (28% vs 4%) and this risk is increased 3 fold if they are SAC/SRC with a positive CMV tissue (PCR and/or histology) (Odds ratio 3.16, 95% CI: 0.74-13.21, 1 p=0.04) (50% colectomy rate vs 6% colectomy rate)
- Presentation with active colitis should ideally include submission of tissue for CMV PCR and histopathology protocol
- Baseline sample submission for virology should include blood for CMV IgM serology
- CMV predominantly reflects reactivation; 100% of all CMV tissue positive patients were treated, resulted as IgG positive
- Negative IgG Serological testing can effectively exclude a diagnosis of CMV colitis
- CMV Serological testing is NOT a useful test; positivity level of 4%
- Faecal CMV PCR can be considered as a ‘supportive diagnostic’ result; positivity level of 3%
- No Standardisation of antiviral regimens or treatment duration; SAC/SRC have a treatment level (Ganciclovir/vanadociclovir) of 81% in those CMV positive tissue (IgM PCR and/or histology) whereas only 8% of those CMV positive non-SAC/SRC with treated with antivirals

Conclusion

It is well established that reactivated herpesvirus CMV has tropism for sites of inflammation. IBD patients with active CMV colitis have CMV detectable in the disease region of the gut (Histology or PCR). The level of CMV detectable may be used as an indicator of ‘CMV disease’ as opposed to ‘CMV infection’ and help with effective clinical management (see Figure 1 above). In IBD patients with a flare of colitis, low level detection of CMV in blood and/or colonic tissue typically indicates reactivation of background virus, whereby higher levels indicate active CMV disease.

This audit has shown:
- CMV replication is usually the result of reactivation rather than primary virus infection, and therefore IBD/CD Patients will have a positive Igg antibody screen. This is the first step in identifying possible CMV infected patients.
- Screening test has a low positivity rate (4%); as most CMV is a result of reactivation. Only if IgG will be detectable.
- Screening test is NOT useful as a diagnostic test and can be misinterpreted as a ‘negative CMV’ result and result further investigation.
- Ideal specimens are colonic tissue for CMV PCR, with/without antiviral therapy.
- Screening test is NOT useful as a diagnostic test and can be misinterpreted as a ‘negative CMV’ result and result further investigation.
- Ideal specimens are colonic tissue for CMV PCR, with/without antiviral therapy.
- Screening test is NOT useful as a diagnostic test and can be misinterpreted as a ‘negative CMV’ result and result further investigation.
- Clear guidance on treatment with antivirals and duration of treatment is required
- Efficient testing and reporting of results is important for effective clinical management.

Table 2: RQIA Audit Results (SAC/SRC - Severe acute colitis/Steroid refractory Colitis)

<table>
<thead>
<tr>
<th>Result</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAC/SRC with a positive CMV tissue (PCR and/or histology)</td>
<td>50%</td>
</tr>
<tr>
<td>Presentation with active colitis</td>
<td>100%</td>
</tr>
<tr>
<td>Baseline sample submission for virology</td>
<td>100%</td>
</tr>
<tr>
<td>Antiviral therapy implemented</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 3: CMV qPCR with results in I/U/ml standardised to WHO International Standards, for blood sample or colonic tissue samples (Altorbio qPCR kit and Roche Flow® PCR system)

Figure 1: Over-simplified Schematic on a proposed stratified approach to distinguish between ‘CMV Disease’ and ‘CMV infection/By-stander’

Figure 2: CMV qPCR with results in I/U/ml standardised to WHO International Standards, for blood sample or colonic tissue samples (Altorbio qPCR kit and Roche Flow® PCR system)

Figure 3: Histopathology CMV staining with classic ‘owl’s Eye’ inclusion bodies,

Acknowledgements

Thank you to RQIA for funding and supporting this audit.

Thank you to the NI IBD Interest group for engagement and support.

References

1. Regional Virus Laboratory, Belfast Health and Social Care Trust, Royal Victoria Hospital, Northern Ireland; Consultant Gastroenterologist(s) from 2BHSCT, 3SHSCT, 4WHSCT, 5SEHSCT, 6NHSCT; 7Consultant Pathologist BHSCT; Allison Lloyd, Heather Lawther, Martina Kelly, Helen Graham (BHSCT); Gayle Martin (SEHSCT); Ruth Hall (SHSCT); Jacqueline Kearns, Louise Scullion (NHSCT); Patricia Mailey (WHSCT)