Benefit of Earlier Anti-TNF Treatment on IBD Disease Complications?

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Abstract

Background: Anti-tumour necrosis factor [anti-TNF] treatment was demonstrated to have disease-modifying abilities in inflammatory bowel disease [IBD]. In this study, we aimed to determine the effect of anti-TNF treatment timing on IBD disease complications and mucosal healing [MH].

Methods: The following IBD-related complications were tested in relation to timing of anti-TNF therapy start in newly diagnosed IBD patients [n = 413]: fistula formation, abscess formation, extra-intestinal manifestations [EIM], surgery, referral to academic centre, and MH.

Results: A total of 85 patients [21%) received anti-TNF (66 Crohn’s disease [CD], 16 ulcerative colitis [UC], 3 inflammatory bowel disease unclassified [IBDU]) of whom 57% [48 patients] were treated < 16 months after diagnosis. Patients receiving anti-TNF early [< 16 months] did not differ from patients receiving anti-TNF late [> 16 months] regarding gender, age, smoking status, and familial IBD. More importantly, patients receiving anti-TNF early did not suffer less IBD-related complications during follow-up as compared with patients started on anti-TNF late, nor was more MH observed. Similar results were obtained when anti-TNF treated patient were stratified more stringently, ie < 12 months [40 patients] vs >24 months [24 patients]. Cox regression analysis showed no beneficial correlations between anti-TNF timing and IBD-related complications. Anti-TNF treated patients achieving MH were 1.1 times less likely to develop EIMs compared with patients who did not achieved MH while on anti-TNF.

Conclusions: This study was unable to confirm a benefit of earlier anti-TNF treatment on IBD disease complications. This could be explained by more aggressive treatment earlier in disease,
resulting in fewer IBD complications. However, it seems more likely that inappropriate selection of patients for therapy leads to suboptimal treatment and subsequently suboptimal outcome.

Keywords: Inflammatory bowel disease; anti-TNF; disease complications

1. Introduction
There is considerable variation in the disease severity and progression in patients suffering from inflammatory bowel diseases (IBD). IBD-related complications associated with severity of disease include extra-intestinal manifestations (EIM) such as arthritis, ocular manifestations, dermatological manifestations, and perianal disease. EIMs may affect up to 35% of IBD patients, whereas the lifetime risk for developing fistulas in patients with Crohn’s disease [CD] is reported to be between 20% and 40%. The overall prevalence of perianal abscesses, fistulas, fissures, and ulcers is reported to be between 25% and 80%. EIM and penetrating disease correspond with an increased burden of disease and decreased quality of life. Patients diagnosed with these IBD-related complications are increasingly treated with drugs at the top of the treatment pyramid. There is increasing evidence that treating patients more aggressively earlier in the disease course will prevent the development of IBD-related complications. This mostly relies on studies implicating anti-tumor necrosis factor [anti-TNF] drugs to have the ability to modify the natural course of the disease. For example, anti-TNF has been demonstrated to induce mucosal healing, which seems to be correlated with long-term disease remission. However, data demonstrating the effect of starting anti-TNF early after diagnosis on limiting IBD-related complications in a population-based setting are lacking.

In this study, we aimed to determine the effect of receiving anti-TNF early as opposed to receiving anti-TNF later on IBD disease complications and mucosal healing. Additionally, we wanted to provide insight into the incidence of IBD complications shortly after diagnosis in a population-based cohort.

2. Methods
2.1. Patient selection
The population-based Delta cohort has been described previously. We included 413 newly diagnosed IBD patients between January 1, 2006 and January 1, 2007 in nine general hospitals in the southwest of The Netherlands. Data on patient and disease characteristics were obtained from the patients’ medical charts.

2.2. Treatment
Early anti-TNF treatment was determined as starting anti-TNF within 16 months after diagnosis, whereas late anti-TNF was determined as starting after 16 months. In addition, for a more stringent stratification, patients receiving anti-TNF < 12 months after diagnosis were compared with patients receiving anti-TNF > 24 months after diagnosis. Concomitant immunosuppressive [IS] treatment was classified as none, partly, or total [treated with IS for > 70% of the time under anti-TNF treatment].

2.3. Patient and disease characteristics
Patients were diagnosed according to the Lennard-Jones criteria for IBD. Disease characteristics were scored according to the Montreal criteria. For each patient, the following baseline characteristics were retrieved: date of birth, comorbidities, smoking status, and familial IBD status. For disease location and characteristics, patients with inflammatory bowel disease unclassified [IBDU] were classified as patients with ulcerative colitis [UC]. All endoscopy, pathology, radiology, and surgical reports were retrieved. Endoscopy and histological reports were scored for disease extension, characteristics, and disease severity according to the Montreal criteria and the Mayo score.

2.4. Statistics
Statistical analyses were performed using descriptive statistics, independent t-tests, Mann-Whitney nonparametric tests, chi square [X²] tests, and Fisher’s exact test. Independent samples t-tests were used to compare means. Proportions were compared using the X² test or Fisher’s exact test. Correlations were assessed using a logistic regression and Cox regression using the enter method expressed as odds ratios [OR] with 95% confidence interval [CI] or hazard ratios [HR] with 95% confidence interval [CI]. Two-sided p-values < 0.05 were considered significant. Statistical analyses were performed using SPSS for Windows software [v21.0, Chicago, IL].

3. Results
In total, 413 IBD patients were included, [201 CD, 188 UC, and 24 IBDU]. The mean age at onset was 38.00 years [14-95]. Of the patients, 218 [52.8 %] were females. Median duration of follow-up was 38.93 months [0.2-47.9]. Overall, 85 patients [20.6%] received anti-TNF treatment.

3.1. IBD treatment
Initial therapy after IBD diagnosis in the Delta cohort has been described before. A total of 66 CD patients [pts] used anti-TNF during follow-up, of whom 52% [34 pts] started this treatment within 12 months after diagnosis and 62% [41 pts] within 16 months after diagnosis. In two CD patients, the decision for anti-TNF was made but they never started the treatment. One of these patients died from an unknown cause before the first administration and one patient had a positive quantiferon test. Of the 66 CD patients receiving anti-TNF, 77.3% [51 pts] received infliximab (IFX), 15.2% [10 pts] received IFX as well as adalimumab [ADA], and 7.5% [5 pts] received ADA only. One patient, after being treated with IFX and ADA earlier, was later started on certolizumab. Sixteen UC patients received anti-TNF, five within 16 months after diagnosis. Eleven UC patients received anti-TNF more than 16 months after diagnosis. However, two patients did not receive the drug for
the primary indication of IBD, but for rheumatoid arthritis [ADA] and ankylosing spondylitis [IFX]. The other 14 patients all received IFX, of whom one later switched to ADA because of side effects of IFX. Three IBDU patients received anti-TNF [all IFX], of whom two patients started within 16 months after diagnosis. More details about anti-TNF use can be found in Table 1. Of the 85 patients treated with anti-TNF, 44 [51.7%] were concomitantly treated with IS and 20 [23.5%] were partly concomitantly treated with IS. An overview of concomitant IS treatment can be found in Figure 1.

3.2. Disease complications
Of the 413 patients in this cohort, 12.8% [53 pts] suffered from penetrating disease. A total of 9.9% [41 pts] were diagnosed with fistulas, of whom 22 patients already suffered from fistulas at diagnosis [20 CD, 2 UC]. Furthermore, 6.8% [28 pts] developed abscesses, of whom 14 patients [12 CD, 2 UC] suffered from abscesses at diagnosis. EIMs were present in 17.7% [73 pts; 52 CD, 20 UC, 1 IBDU] of the patients in our cohort. A detailed differentiation of the EIMs can be found in Table 2.

3.3. Surgery
Within follow-up, 13.8% of the newly diagnosed IBD patients [57 pts] underwent IBD-related surgery. The overall median time to surgery was 2.46 months [mean 10.71 months, range 0–46.26]. Of the CD patients, 23.4% [47 pts] underwent 78 IBD-related surgical procedures, 36 [46%] of which were resections. The mean time to IBD-related surgery in CD patients was 6.95 months [median 0.53 months]. Ten UC patients [17.5%] underwent 18 surgical procedures [19.4% of all surgeries], in whom the median time to surgery was 33.2 months [mean 28.6, range 2.3–46.4]. An overview of all surgical procedures can be found in Table 3.

Table 1. Details of response to anti-TNF treatment.

<table>
<thead>
<tr>
<th></th>
<th>IFX [n = 79]</th>
<th>ADA [n = 17]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose escalation</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Dosing more frequently</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Dosing less frequently</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Dosing more frequent after being dosed less frequently</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Side effects</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Stop due to side effects</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Antibodies</td>
<td>n.a.</td>
<td>1</td>
</tr>
<tr>
<td>Stop treatment</td>
<td>42</td>
<td>3</td>
</tr>
<tr>
<td>Primary non-response</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Clinical sustained remission</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>Continuous use till end follow-up</td>
<td>37</td>
<td>14</td>
</tr>
</tbody>
</table>

Table 2. Extra-intestinal manifestations in the Delta Cohort.

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Total [n = 413]</th>
<th>Anti-TNF [n = 85]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess</td>
<td>28 [6.8%]</td>
<td>13 [15.3%]</td>
</tr>
<tr>
<td>Arthritis</td>
<td>25 [6.1%]</td>
<td>11 [12.9%]</td>
</tr>
<tr>
<td>Aphtous stomatitis</td>
<td>9 [2.2%]</td>
<td>5 [5.9%]</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>8 [1.9%]</td>
<td>5 [5.9%]</td>
</tr>
<tr>
<td>Fistula</td>
<td>41 [9.9%]</td>
<td>22 [25.9%]</td>
</tr>
<tr>
<td>Abdominal</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Perianal</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>Fissures</td>
<td>14 [3.4%]</td>
<td>4 [4.7%]</td>
</tr>
<tr>
<td>Ocular involvement</td>
<td>8 [1.9%]</td>
<td>3 [3.5%]</td>
</tr>
<tr>
<td>Liver</td>
<td>1 [0.3%]</td>
<td>0</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>5 [1.3%]</td>
<td>2 [2.4%]</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

All numbers are presented as number of patients, n [%].

Table 3. Surgical procedures.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Total [n = 413]</th>
<th>Anti-TNF [n = 85]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileocecal resection</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Colon resection</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Proctectomy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mucosectomy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Small bowel resection</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Right hemicolectomy with resection of ileum</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Isolated part colon and isolated part small bowel</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Stoma surgery</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Abscess and fistula surgery</td>
<td>19 [plus 13 before diagnosis]</td>
<td>10 [plus 2 before diagnosis]</td>
</tr>
<tr>
<td>Abdominal exploration without bowel resection</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Appendectomies</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Other IBD surgery-linked reasons</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Abscess drainage under radiology</td>
<td>15</td>
<td>3</td>
</tr>
</tbody>
</table>

All surgical procedures in the Delta cohort from diagnosis until end of follow-up.

All numbers are presented as numbers of procedures.

Anti-TNF, anti-tumour necrosis factor; IBD, inflammatory bowel disease.
3.4. Treatment vs outcome

The median follow-up of anti-TNF treated patients was 41.4 months [range 15.5 – 47.9]. Of the 85 patients receiving anti-TNF, 48 did so within the first 16 months after diagnosis. More CD patients received anti-TNF compared with UC + IBDU patients [p = 0.002] and more CD patients received early anti-TNF [p = 0.05]. Patients receiving anti-TNF early [<16 months] did not differ from patients receiving anti-TNF late [> 16 months] regarding gender, age, smoking status, and familial occurrence of IBD. More importantly, patients receiving anti-TNF early did not suffer less EIMs, IBD-related surgery or resection, fistulization, or abscess formation, during follow-up as compared with patients who were started on anti-TNF late. Removing ileocaecal resections out of the analysis did not result in differences in surgery and resection rates between the groups. Similar results were obtained when patient groups were stratified more stringently, ie < 12 months [40 pts, 34 CD, 3 UC, 3 IBDU] to anti-TNF vs 24 months to anti-TNF treatment [23 pts, 16 CD, 7 UC], with the exception of referrals to an academic centre, which occurred more often in patients receiving anti-TNF < 12 months after diagnosis [p = 0.030]. When analysing the development of complications after the administration of anti-TNF, early anti-TNF receivers developed more fistulas compared with patients receiving anti-TNF late [p = 0.014], which was also the case in the stringent separation [p = 0.012]. In a logistic regression analysis, a correlation between anti-TNF early vs late and fistula formation after TNF administrations was found, showing a protective effect of late anti-TNF [OR 0.11, CI 0.01–0.087]. However, there were no differences in the amount of fistulas before starting anti-TNF, either between patients receiving anti-TNF < 16 months vs > 16 months, or between patients receiving the drug < 12 months vs > 24 months. A Cox regression analysis was performed in order to correct for the time of complication occurrence. Analysis of a possible correlation between the overall time to anti-TNF and the occurrence of complications, showed no correlations regarding EIMs, resections, overall IBD surgery, abscess formation, fistula formation, or referral to an academic centre. Thus no indication of a beneficial effect of earlier anti-TNF over late anti-TNF was found. A comparison of the complication-free survival between early and late treated anti-TNF patients can be found in Figure 2.

As there is not enough evidence for an equal effect of IFX in UC patients compared with CD patients, an additional analysis in CD patients only was performed; but again, no differences were found between patients receiving anti-TNF early vs late, either using the 16 months cut-off, or using the < 12 months, > 24 months stratification.

Lastly, as using IS concomitant with anti-TNF is believed to further improve disease outcome, we corrected our findings for concomitant IS use, as more patients using anti-TNF early were concomitantly treated with IS [p < 0.0001 in < 16 months vs > 16 months, and p = 0.02 in < 12 months vs. > 24 months]. We again were unable to prove differences between using early vs late anti-TNF regarding abscesses or fistula formation, EIMs, surgery, resection, or referral to academic centres.

3.5. Mucosal healing

MH status could be determined in 227 of 412 patients; 40 of these patients [17.6%, 19 CD, 18 UC, 3 IBDU] showed MH. In 74 of the 85 patients treated with anti-TNF, MH status could be determined, and in five patients [6.8%, 4 CD, 1 IBDU] MH was seen during endoscopy. When comparing the < 16 with the > 16 group, there was a difference in the amount of patients undergoing a second endoscopy [p = 0.014]. However, this difference disappeared when using the more stringent criteria [< 12 vs > 24 months, p = 0.08]. Furthermore there were differences in the time to second endoscopy when comparing the early treated with the late treated group [<16 vs >16, p = 0.024, <12 vs >24, p = 0.006].

There were no differences in the amount of patients achieving MH in the < 16 months vs > 16 months group [p = 0.18], nor when comparing the < 12 months and > 24 months groups [p = 0.22]. Considering the small amount of anti-TNF treated patients achieving mucosal healing, we were unable to further analyse differences between patients achieving anti-TNF early and patients achieving anti-TNF late.

4. Discussion

Overall, one-third of newly diagnosed IBD patients in the Delta cohort experienced an IBD-related complication in the first few years after diagnosis. Close to one-fifth had EIMs, 13% had fistulas or abscesses, and 14% required surgery. Additionally, 21% of newly diagnosed IBD patients started on anti-TNF within the first few years after diagnosis, of whom almost half did so within the first year. We were unable to find a beneficial effect of starting anti-TNF early compared with starting anti-TNF late with respect to the occurrence of disease complications, mucosal healing, and surgery.

Population-based data regarding the short-term incidence of fistulas and abscesses are also scarce. The peak incidence of perianal lesions is shown to be around the time of diagnosis, with incidence rates ranging from 2–18%. Previously published studies regarding cumulative incidence of fistulas and abscesses report 1.4% of UC patients to have fistulas within the first 5 years after diagnosis and 0.6% to have abscesses, and 8.5% of the CD patients to suffer from fistulas within the first 5 years after diagnosis and 12.3% patients to have abscesses. These results are similar to the incidences we found in the Delta cohort.

The reported lifetime risk for the development of IBD-related EIMs ranges from 6% to 47%. Previously published cohorts report an incidence of extra-intestinal manifestations at diagnosis ranging between 15% and 27%. There is little known about the cumulative incidence of extra-intestinal manifestations in relation to the IBD disease duration, which precludes direct comparison of the EIM incidence in our cohort with reported numbers. Compared with cohort studies which do mention EIMs in follow-up, we seem to find fewer EIMs in follow-up. We were unable to identify one particular reason for this, as there were many methodological differences. Our cohort was created in a population-based manner, with an enrolment of all consecutive newly diagnosed IBD patients. We therefore do not expect to have missed many extra-intestinal manifestations. However, immunosuppressant and anti-TNF treatment rates are higher in our cohort compared with previously published studies, which might contribute to our lower EIMs incidence rate.

Among published studies, surgical resection rates vary widely over time, ranging from 25% to 61% at 5 years. The incidence of IBD-related surgery is known to have a peak in the first years after diagnosis but remaining stable afterwards. Indeed, we confirmed a relatively high incidence of IBD-related surgery when compared with the ICURE cohort. Another cohort, reporting cumulative resection rates, reports an incidence of 12% in CD patients and 6% in UC within the first year in patients diagnosed in 2003–2004. This is comparable to the rates in the CD patients in the Delta cohort, but UC patients had less resections in their first year after diagnosis. However, again, in the reported study fewer patients were treated.
Is Earlier Anti-TNF Beneficial?

Figure 2. Anti-TNF and concomitant IS use. TNF, tumour necrosis factor; IS, immunosuppression.

with anti-TNF compared with our cohort [5% CD and 1% UC vs 32.8% CD and 8.5% UC in the Delta cohort].

A few limitations are to be mentioned regarding our study. First, this study was conducted retrospectively. In 224 of 413 patients, mucosal healing could be determined. It is more likely that patients underwent an endoscopy because of limited response to therapy or because of disease worsening, than to determine mucosal healing. Therefore MH rates might actually be higher than we are able to report here. However, a relatively high percentage of patients receiving anti-TNF underwent a second endoscopy [74 of 85 pts]. The numbers of anti-TNF treated patients achieving MH was low, but these data show that mucosal healing is not limited to either one of the anti-TNF treatment strategies. However, considering this small amount of anti-TNF treated patients achieving mucosal healing, we were unable to further analyse differences between patients achieving anti-TNF early and patients achieving anti-TNF late.

Additionally, there is no consensus regarding the definition of ‘early treatment’. In our cohort, we used two definitions of early treatment, but neither showed a beneficial effect over starting treatment later. The patients in our cohort developed less disease complications and also used more IS and anti-TNF when compared with previously published cohorts. This could be an indication that the patients in the Delta cohort might be treated more aggressively earlier on, which influences outcome.

Anti-TNF has been shown to have disease-modifying abilities. However, we were unable to detect such an effect in our cohort, as there were no differences in total disease outcome or mucosal healing between patients starting anti-TNF early or late, nor between patients receiving anti-TNF vs patients not receiving anti-TNF. In contrast, we observed that patients who start anti-TNF early are more likely to develop fistulas afterwards, in contrast to the step-up top-down study by Baert et al. This unexpected outcome could not be explained by preexistent fistulas before start of treatment. The Cox regression analysis did not show differences in the amount of fistulas after anti-TNF administration. This might indicate that the limits of the therapeutic arsenal are reached sooner in patients who start anti-TNF earlier. Another explanation might be that patients starting anti-TNF early indeed show a more complicated disease course. However, as there were no other differences in disease complications between the groups, this does not seem likely at this point in disease follow-up.

Theoretically it is conceivable that the indication for early start of anti-TNF therapy is linked to the development of fistulas, whereas treatment of patients with anti-TNF late is due to failure of previous treatment or progression of the disease itself. However, there was no difference in the overall amount of patients suffering fistulas in the early vs the late group, nor in the amount of patients developing fistulas before the start of anti-TNF treatment.

We were unable to detect parameters related to anti-TNF therapy timing. It seems that patients are sometimes started on anti-TNF based on ‘gut feeling’ or ‘instinct’ of physicians. Unselected administration of treatment might result in patients who would benefit from early anti-TNF ending up in the late anti-TNF group and vice versa. With this, an overall picture is emerging in which anti-TNF is given as a last resort to patients with perceived disease severity rather than to patients who are most likely to benefit from this treatment. We previously found disappointing durable remission rates in complex Crohn’s disease fistulas. In this study we see that, even when corrected for disease severity at diagnosis, not receiving anti-TNF makes patients more likely to achieve mucosal healing, which contrasts with previous studies. This, alongside our finding that anti-TNF treated patients who do achieve MH are less likely to develop EIMs, strengthens the idea that inappropriate selection of patients, rather than early anti-TNF administration, is related to this disappointing effect of anti-TNF treatment.

In conclusion, we were unable to confirm a benefit of earlier anti-TNF treatment on the amount of IBD disease complications in our patients. It seems that in the Delta cohort, treatment strategies differed from earlier studies, with patients being treated more aggressively earlier on, resulting in less development of IBD complications and a population too homogeneous to detect differences in outcome. However, it is also possible that inappropriate selection of patients for a specific therapy led to a suboptimal drug efficacy, lacking the ability to modify the natural course of the disease and prevent the development of disease complications. Future research should aim to distinguish between these two possibilities and elucidate the appropriate method for selecting patients with an undesirable IBD disease outcome.
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Conflicts of Interest
VN received an unrestricted educational grant from Dr. Falk Benelux B.V. KB has received consultancy fee from MSD. LP-B is a board member of Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillotts, Vifor, Therakos Pharmacosmos, Pilege, BMS, UCS-pharma, and Hospira; and has received grants from Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillotts, Vifor, Therakos Pharmacosmos, Pilege, BMS, UCS-pharma, Hospira, Shire, Genentech, Mitsubishi, Celltrion, Boehringer-Ingelheim, HAC-pharma, and Takeda. JW has received consultancy fees from MSD, Abbvie, Pharmacosmos, and Ferring and an unrestricted educational grant from Dr. Falk Benelux B.V.

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Author Contributions
VN, literature search, study format, writing protocol, collecting data, processing data, data interpretation, analysing data, figures, writing manuscript; GE, literature search, data interpretation, commenting on manuscript and writing manuscript; ME, literature search, collecting data, processing data; RO, identification of cases, provision of patient data, data interpretation; MR, identification of cases and provision of patient data; RB, identification of cases, providing patient data, data interpretation, RQ, identification of cases, providing patient data, data interpretation; AT, identification of cases, providing patient data, data interpretation; KB, identification of cases, providing patient data, data interpretation; HL, identification of cases, providing patient data, data interpretation; LP-B, literature search, study format, data interpretation, commenting on manuscript, writing manuscript; JW, literature search, study format, writing protocol, data interpretation, commenting on manuscript and writing manuscript.

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