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Anti-TNF use in inflammatory bowel disease
Geriatric assessment prior to geriatric rehabilitation
Temozolomide in metastasised pituitary carcinoma
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EDITORIAL

Why a case report is more than just an unexpected observation

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Clinical trials only detect frequently occurring adverse events, and the detection of rarer adverse events depends on experience gained during the period after marketing of a drug. At this point in time the drug is used under real-life circumstances and in large groups of patients. Although post-marketing clinical studies are also designed to study safety, there is a key role for reporting presumed adverse events. Reporting of serious adverse events to the local regulatory authorities (e.g. Netherlands Pharmacovigilance Centre Lareb in the Netherlands) is required by law, also outside clinical trials. However, case reports with adverse events published in medical literature also form an important contribution to pharmacovigilance. After all, the publication of the first report on congenital deformations after maternal use of thalidomide, published in the Lancet in 1961, stood at the beginning of drug safety legislation and the formation of the regulatory authorities that we know today. Nowadays, almost 60 years later, spontaneous reports are still vital in decision-making during the life cycle of a drug after marketing. Nineteen drugs were withdrawn from the European market between 2002 and 2011 for safety reasons, based on information mostly provided by case reports. Reports on adverse events are not only important for monitoring the safety profile of a drug, but can also give insight into pharmacological pathways and the mechanism of action of a drug. This helps to clarify our understanding of the pathophysiology of certain diseases.

In this issue of the Netherlands Journal of Medicine, Muller-Hansma and colleagues present a case of an adolescent boy who was diagnosed with acute lymphoblastic leukaemia for which he was treated with dasatinib, a tyrosine kinase inhibitor (TKI). During this treatment he developed proteinuria, oedema and hypalbuminaemia; events that were already listed in the product leaflet of dasatinib. Recently, nephrotic syndrome was added. One could argue that the presented case does not fulfil all the criteria for nephrotic syndrome, since the reported proteinuria is not in the nephrotic range (<3.5 grams/24 hours). However, the clinical symptoms in this case in combination with the presented spontaneous reports from Eudravigilance and case reports from literature do provide sufficient support to include nephrotic syndrome as a separate adverse event.

In the presented case, the time course and the swift recovery of the symptoms when the drug was stopped contributes to a high likelihood of causality. It is likely that nephrotic syndrome is a class effect of the TKIs, since it has been described in other TKIs, such as imatinib and sunitinib, as well. A clear hypothesis on the pathophysiological pathway linking treatment with TKIs and nephrotic syndrome exists through its effect on vascular endothelial growth factor (VEGF). Anti-VEGF treatment affects VEGF production, and results in endothelial damage and loss of nephrin. The resulting malfunction of the glomerular filtration apparatus will ultimately lead to the development of nephrotic syndrome. Nephrotic syndrome has also been associated with the use of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) in the treatment of metastatic melanoma, in which VEGF inhibition also plays an important role. These types of reports help in understanding the pathophysiology of the adverse events associated with targeted therapies.

Not only the treatment of a malignancy may be associated with the development of nephrotic syndrome, but the malignancy itself can cause glomerular disease including nephrotic syndrome as well. Chronic lymphocytic leukaemia, for which dasatinib is registered, is associated with membranoproliferative glomerulonephritis and nephrotic syndrome. Treatment options in oncology have increased in the last decades. TKIs are increasingly prescribed, but also...
the use of immunotherapy is emerging. In both, renal adverse events including nephrotic syndrome have been reported.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)
In most cases of nephrotic syndrome associated with treatment with TKIs, symptoms resolved spontaneously after discontinuing the drug, and further treatment was not necessary. Renal adverse events in nivolumab and pembrolizumab (both PD-1 inhibitors), both examples of immunotherapy, however, may need immunosuppressive treatment, depending on the severity of the symptoms.\(^1\)\(^2\)\(^3\) Screening for immunological adverse events, including nephritis, is standard care during these treatments.

With the increasing use of targeted therapies, clinicians should be aware of the development of new types of adverse events which may also affect the kidney. The introduction of these targeted therapies for a broad spectrum of diseases has involved prescribers from many different medical backgrounds. Awareness of the potential for localized and sometimes atypical adverse events may not always be present. Due to the fact that case reports are typically descriptions of small numbers of observations, without ingenious methodological study design or statistical analysis, they are at the bottom of the hierarchy of clinical evidence. However, as illustrated with the examples on nephrotic syndrome, we emphasise that case reports do have an important role in medical research and continuous medical education.

**REFERENCES**

Nephrotic syndrome under treatment with dasatinib: be aware of a possible adverse drug reaction

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ABSTRACT

The protein kinase inhibitor dasatinib, targeting BCR-ABL and Src family kinases, is used in chronic myeloid leukaemia and Philadelphia-chromosome positive acute lymphoblastic leukaemia. The Netherlands Pharmacovigilance Centre Lareb has received one report of nephrotic syndrome associated with the use of dasatinib. With some other protein kinase inhibitors, targeting vascular endothelial growth factor, nephrotic syndrome is a well-known adverse drug reaction. The Dutch and European pharmacovigilance databases and scientific literature contain several cases indicating a causal relationship between dasatinib and nephrotic syndrome. Nephrotic syndrome was recently added to the list of adverse drug reactions in the Dutch summary of product characteristics for dasatinib. It is important to recognise the possibility of this adverse drug reaction when a patient develops nephrotic syndrome under treatment with dasatinib.

KEYWORDS

Adverse drug reaction, dasatinib, nephrotic syndrome

INTRODUCTION

Dasatinib (Sprycel®) is indicated in adults for newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukaemia (CML). Ph+ acute lymphoblastic leukaemia (ALL) and CML in the chronic, accelerative or blastic phase resistant to previous therapy including imatinib. Dasatinib belongs to the group of protein kinase inhibitors. The mechanism of action is inhibition of BCR-ABL-kinase, kinases from the Src family and several other oncogenetic kinases including c-KIT, ephrin receptor kinases and PDGFβ receptor. Dasatinib was granted marketing authorisation in the Netherlands in 2006.1 CML is a myeloproliferative neoplasm, with in general three disease phases: the chronic phase, the accelerated phase and the blast crisis.2 ALL is a lymphoid neoplasm which shows a progressive disease course, where symptoms may progress over weeks to months with others presenting even more acutely. The Philadelphia (Ph) chromosome refers to a balanced translocation between chromosomes 9 and 22 that can be present in CML and ALL, resulting in BCR-ABL1 fusion, with different breakpoints giving rise to a p190 and p20 protein. Subsequent BCR-ABL1 activity promotes uncontrolled proliferation of transformed cells.2,3 Nephrotic syndrome can have various causes and is defined by the presence of heavy proteinuria (protein excretion > 3.5 g/24 hours), hypoalbuminaemia (< 30 g/l), and peripheral oedema. Proteinuria results from defects in the capillary wall of the glomeruli, which consists of the fenestrated capillary endothelium, the glomerular basement membrane and the podocytes (the epithelial cells in the glomeruli).4 This article describes cases concerning dasatinib associated with nephrotic syndrome from the spontaneous reporting database in the Netherlands maintained by the Netherlands Pharmacovigilance Centre Lareb, the European Pharmacovigilance database EudraVigilance maintained by the European Medicines Agency (EMA), and cases published in scientific literature. It must be noted that cases from pharmacovigilance databases concern spontaneous reports of possible adverse
drug reactions reported by healthcare professionals, manufacturers, patients or others, and the likelihood of a causal relationship can differ between cases.

CASE SERIES

The detailed cases are described below. A summary of the cases is listed in table 1.

Case received by Lareb
The Netherlands Pharmacovigilance Centre Lareb received one report of nephrotic syndrome with the use of dasatinib, after initial treatment with imatinib which was poorly tolerated (muscle and joint pain). The patient was a male in the age group 11-20 years with Ph+ ALL, who developed nephrotic syndrome (oedema with a weight gain of 6 kg, proteinuria with a protein-creatinine ratio 126.7 mg/mmol, and hypoalbuminaemia with a blood albumin of 12 g/l), 27 days after starting dasatinib 60 mg/m² once daily. Dasatinib was withdrawn and fluid intake restricted. One week after withdrawal of dasatinib the patient had recovered from the nephrotic syndrome. Previous treatment included cytarabine and mercaptopurine; the Dutch summaries of product characteristics (SmPCs) for these drugs do not report nephrotic syndrome or proteinuria as adverse reactions. No other potential causes were identified either. After dasatinib was withdrawn the patient was switched back to imatinib and nephrotic syndrome has not recurred since.

EudraVigilance cases
The European Pharmacovigilance database EudraVigilance contained another seven strongly supportive cases of dasatinib associated with nephrotic syndrome. All seven cases concerned female patients. One case was a patient under the age of 18 years, the other cases were all adults. The mean age was 42 years. The latencies varied from about one month to seven months and one patient had a longer latency of almost five years. In one case latency was not reported. In six cases dasatinib was withdrawn and in one case the dose was decreased. Six patients recovered or were recovering from the reaction at the moment of reporting, and in one report the outcome was unknown. In one case it was reported that slight recovery after temporary interruption of dasatinib was followed by recurrence of the reaction after resumption of dasatinib, and again by recovery after withdrawal of dasatinib. In one patient treatment other than withdrawal of dasatinib for the nephrotic syndrome was reported. In two reports results from renal biopsy were specifically described: in one case focal segmental glomerulosclerosis was seen and in one case focal and segmental hyalnosis. In one report membranous glomerulonephritis was reported as reaction without mentioning whether this was biopsy-proven.

Cases in scientific literature
The scientific literature describes five other patients with nephrotic syndrome associated with dasatinib use. A nine-month-old girl was diagnosed with Ph+ CML. She was treated with imatinib for a year and was then switched to dasatinib 60 mg/m² because of BCR-ABL positivity. At the age of three years she developed nephrotic syndrome. Electron microscopy of a renal biopsy showed partial glomerular epithelial foot process effacement and focal capillary loop collapse with basement membrane wrinkling. She was treated and the reaction improved, but the patient only recovered from the reaction after withdrawal of dasatinib. A five-year-old boy with Ph+ ALL developed nephrotic syndrome 26 days after haematopoietic stem cell transplantation while using dasatinib (dose not reported). At electron microscopy most podocytes foot processes were fused, which could indicate minimal change disease. Within a week after withdrawal of dasatinib, the nephrotic syndrome resolved.

A 63-year-old woman with CML experienced nephrotic-range proteinuria, while using dasatinib 100 mg/day. Kidney biopsy showed evidence of chronic thrombotic microangiopathy. The patient recovered from the proteinuria after switching to imatinib.

A 64-year-old woman with Ph+ ALL used dasatinib in addition to a regimen of chemotherapy comprising cyclophosphamide, daunorubicin, vincristine, prednisolone, methotrexate, cytarabine and dexamethasone. Two weeks after the dose of dasatinib was increased from 110 mg to 140 mg daily, she developed nephrotic syndrome. After withdrawal of dasatinib the nephrotic syndrome resolved within a week. Dasatinib was restarted in a lower dose of 70 mg daily without recurrence of nephrotic syndrome.

One literature case was described in the EudraVigilance database, but the original article was not available through PubMed. This case concerned a male in the age group 11-20 years with Salmonella sepsis and nephrotic syndrome receiving treatment with dasatinib 60 mg/m² for ALL with a latency of ten months. The reaction was treated with fluid restriction, diuretics and albumin infusions. Five weeks later the patient developed chylothorax. Dasatinib was withdrawn and a low-fat diet was started. Within two weeks, the chylothorax resolved. Dasatinib was restarted at a reduced dose of 48 mg/m²/day instead of 60 mg/m² without recurrence of nephrotic syndrome and chylothorax.
Table 1. *Cases of nephrotic syndrome associated with dasatinib in the Lareb database*, scientific literature8-13 and *EudraVigilance database*12

<table>
<thead>
<tr>
<th>Source</th>
<th>Age group (years)</th>
<th>Gender</th>
<th>Indication</th>
<th>Latency</th>
<th>Kidney biopsy</th>
<th>Reported intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lareb database</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11-20</td>
<td>Male</td>
<td>Ph+ ALL</td>
<td>25 days</td>
<td>Not reported</td>
<td>Withdrawal of dasatinib, Antibiotics, analgesics, immunoglobulins, fluids, parenteral nutrition</td>
<td>Recovered one week after withdrawal of dasatinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EudraVigilance database</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>41-50</td>
<td>Female</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Biopsy not reported, but membranous glomerulo-nephritis was reported as reaction</td>
<td>Withdrawal of dasatinib</td>
<td>Recovering</td>
</tr>
<tr>
<td></td>
<td>61-70</td>
<td>Female</td>
<td>CML</td>
<td>About four months</td>
<td>Focal segmental glomerulo-sclerosis</td>
<td>Withdrawal of dasatinib</td>
<td>Recovering</td>
</tr>
<tr>
<td></td>
<td>31-40</td>
<td>Female</td>
<td>CML</td>
<td>About one month</td>
<td>Focal and segmented hyalinosis</td>
<td>Dose reduction of dasatinib, Prednisone, irbesartan</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>31-40</td>
<td>Female</td>
<td>CML</td>
<td>Four years and eight months</td>
<td>Partial glomerular epithelial foot process effacement and focal capillary loop collapse with basement membrane wrinkling</td>
<td>Prednisone, ACE inhibitor</td>
<td>Recovered</td>
</tr>
<tr>
<td></td>
<td>41-50</td>
<td>Female</td>
<td>CML</td>
<td>About six months</td>
<td>Not reported</td>
<td>Withdrawal of dasatinib</td>
<td>Recovered</td>
</tr>
<tr>
<td></td>
<td>11-20</td>
<td>Female</td>
<td>CML</td>
<td>Eleven to twelve weeks</td>
<td>Not reported</td>
<td>Withdrawal of dasatinib</td>
<td>Recovered in ten days</td>
</tr>
<tr>
<td></td>
<td>41-50</td>
<td>Female</td>
<td>CML</td>
<td>Seven months</td>
<td>Not reported</td>
<td>Temporary interruption, followed by resumption, followed by withdrawal of dasatinib</td>
<td>Slight recovery after interruption, recurrence after resumption, recovering after withdrawal</td>
</tr>
</tbody>
</table>

**Scientific literature [Reference]**

[8] 3 Female Ph+ CML About one year Partial glomerular epithelial foot process effacement and focal capillary loop collapse with basement membrane wrinkling Prednisone, ACE inhibitor, Only recovery after withdrawal of dasatinib Recovered

[9] 5 Male Ph+ ALL Not reported Most foot processes were fused Withdrawal of dasatinib Recovered within a week

[10] 63 Female CML Not reported Evidence of chronic thrombotic microangiopathy Withdrawal of dasatinib, Lisinopril, pravastatin Recovered

[11] 64 Female Ph+ ALL Two weeks after dose increase Not reported Prednisolone, Withdrawal of dasatinib, followed by restart of dasatinib at a lower dose Recovered within a week after withdrawal of dasatinib, no recurrence after restart of dasatinib at a lower dose

[12,13] 11-20 Male ALL Ten months Not reported Withdrawal of dasatinib, followed by restart at a lower dose, Fluid restriction, diuretics, albumin, low fat diet Recovered
**DISCUSSION**

A possible mechanism of how dasatinib might cause nephrotic syndrome is disruption of the vascular endothelial growth factor (VEGF) signalling pathway through inhibition of the Src family kinases, one of the targets of dasatinib. VEGF expression occurs in human podocytes and is involved in maintaining normal glomerular function. Disrupting VEGF signalling through therapy targeting VEGF or through inhibition of the VEGF receptors is associated with minimal change nephrotic syndrome which may evolve to focal and segmental glomerulosclerosis, and thrombotic microangiopathy in the glomerular and peritubular capillaries. Proteinuria after inhibition of VEGF signalling is considered a dose-related side effect. The Dutch SmPC for dasatinib mentions proteinuria as a sometimes occurring adverse reaction and nephrotic syndrome was also recently added to the list of adverse reactions, with unknown frequency of occurrence. In the Dutch SmPCs of the Src family kinase inhibitor bosutinib and the BCR-ABL kinase inhibitors imatinib, nilotinib and ponatinib, neither nephrotic syndrome nor proteinuria are mentioned as adverse reactions. Concerning other tyrosine kinase inhibitors nephrotic syndrome is a labelled adverse reaction for sorafenib and sunitinib, both drugs with therapeutic targets that include VEGF receptors. Based on the report received by Lareb, the other cases in EudraVigilance database, maintained by the European Medicines Agency (EMA). The opinions and conclusions, however, are not those of the various centres, nor of the EMA. The information originates from a variety of sources, and the likelihood that the suspected adverse reaction is drug related can vary between cases.

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CMZ declares research collaboration with Novartis, BMS and Pfizer for paediatric development of tyrosine kinases. The other authors have no conflicts of interest to declare.

**DISCLAIMER**

The authors are indebted to the national pharmaco-vigilance centres that contributed data to the EudraVigilance database, maintained by the European Medicines Agency (EMA). The opinions and conclusions, however, are not those of the various centres, nor of the EMA. The information originates from a variety of sources, and the likelihood that the suspected adverse reaction is drug related can vary between cases.
Patterns of anti-TNF use and associated treatment outcomes in inflammatory bowel disease patients: results from an analysis of Dutch health insurance claims data

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ABSTRACT

Introduction: Real-life patterns of anti-tumour necrosis factor (anti-TNF) use remain largely unknown. We aimed to investigate survival rates, clinical outcomes and costs of anti-TNF agents in a large population of patients with inflammatory bowel disease (IBD).

Methods: Health insurance data from 22,082 IBD patients were provided by Achmea Healthcare. Time to anti-TNF discontinuation, treatment intensification, corticosteroid initiation and hospitalisation were analysed in patients starting on anti-TNF treatment from January 2008 until December 2014. Treatment regimens were analysed at different time points.

Results: In this cohort, 855 and 1199 subjects started infliximab and adalimumab treatment, respectively. The median time to anti-TNF discontinuation was 600 days (IQR 156-1693). The proportion of subjects receiving intensified treatment increased over time (infliximab at 3 vs. 24 months: 22.2% vs. 33.6%, p = 0.01; adalimumab at 3 vs. 24 months: 10.5% vs. 19.3%, p < 0.001). Cessation of anti-TNF treatment was less common in Crohn’s disease patients (HR 0.79, p = 0.001) and in patients receiving intensified treatment (HR 0.62, p = 0.001). Immunomodulator use was associated with a longer time to corticosteroid initiation (HR 0.80, p = 0.048), but not with longer drug survival (HR 0.99, p = 0.617). Hospitalisation was more common in Crohn’s patients (HR 1.49, p = 0.011). Corticosteroid initiation was lower in Crohn’s patients (HR 0.57, p < 0.001) and in patients using infliximab (HR 0.55, p < 0.001).

Conclusions: Discontinuation of anti-TNF therapy occurred earlier than previously reported and was associated with a diagnosis of ulcerative colitis and non-intensified anti-TNF treatment. Immunomodulator use at the start of anti-TNF treatment was associated with a longer time to corticosteroid initiation, but not with longer drug survival.

KEYWORDS

Anti-TNF agents, health insurance database, inflammatory bowel disease, pharmacoeconomics, real-world analysis

INTRODUCTION

The introduction of anti-tumour necrosis factor (anti-TNF) antibodies has revolutionised the therapy of Crohn’s disease and ulcerative colitis, collectively known as inflammatory bowel disease (IBD). Anti-TNF agents are able to induce and maintain remission in IBD patients.¹⁻⁶ Infliximab was registered in the Netherlands for Crohn’s disease in 1999 and for ulcerative colitis in 2006 and adalimumab was registered in the Netherlands for Crohn’s disease and ulcerative colitis in 2007 and 2012, respectively.

The clinical management of IBD patients with anti-TNF agents is complicated by primary and secondary non-response. Approximately 30% of patients do not respond to anti-TNF induction therapy (primary non-responders),⁷ and up to half of initial responders...
will gradually lose response over time (secondary non-responders).\textsuperscript{1,8-11} Primary and secondary non-response are related to low serum drug concentrations and the development of anti-drug antibodies.\textsuperscript{12,13} The proportion of IBD patients with a durable response to anti-TNF treatment in a real-life setting has been investigated in relatively small cohorts.\textsuperscript{10,11}

Several strategies are used to prevent and treat primary and secondary non-response to anti-TNF agents. Firstly, combination therapy (consisting of an anti-TNF agent combined with an immunomodulator) is more effective compared with anti-TNF monotherapy,\textsuperscript{22} which can (at least partly) be explained by reduced anti-drug antibody formation.\textsuperscript{21} Secondly, loss of response can often be managed by increasing the dose and/or decreasing the dosing interval of the anti-TNF agent.\textsuperscript{24} Thirdly, loss of response to anti-TNF agents, especially when this is related to anti-drug-antibody formation, can be overcome by switching to another anti-TNF agent,\textsuperscript{26} or by adding an immunomodulator if a patient is receiving anti-TNF monotherapy.

It is unknown how many IBD patients receive combination therapy and how often anti-TNF treatment is intensified in daily practice. Furthermore, associated treatment outcomes and drug costs of anti-TNF agents in a large real-life population are relatively unknown. Van der Valk et al. studied IBD health care and medication costs in a Dutch cohort of 2252 patients in 2011.\textsuperscript{19} Bernstein et al. assessed costs of IBD management in a large real-life Canadian cohort in 2005 and 2006, but they did not specifically focus on anti-TNF use and related treatment outcomes.\textsuperscript{24} The aim of the present study was to investigate: (i) drug survival rates of anti-TNF agents, (ii) clinical outcomes of anti-TNF therapy, and (iii) drug costs of TNF blockers in a large population consisting of approximately 22,000 Dutch IBD patients.

METHODS

Database
Health insurance claims data were provided by Achmea Healthcare, the largest health insurance provider in the Netherlands. Data were available from 2008 to 2014 on approximately 2.7 million insured persons in 2008, gradually increasing to approximately 4.2 million insured persons in 2014. This population is a representative sample of the urbanised area of the Netherlands.\textsuperscript{25}

Data collection
The following data were collected from subjects who received IBD-related healthcare between 2008 and 2014 (observation period).

Background information: year of birth, gender, number of days insured by Achmea per year, year of death (if applicable), start and stop date of the insured period.

IBD-related healthcare: diagnosis (Crohn’s disease or ulcerative colitis) and treatment setting (inpatient or outpatient).

IBD-related medication use: administration/dispensation date, dose and costs of infliximab, adalimumab, corticosteroids (prednisone or budesonide), thiopurines (azathioprine, 6-mercaptopurine or 6-tioguanine) and methotrexate. Data on infliximab use was available from 2012 to 2014 due to a different reimbursement system before 2012. Prior to 2012, infliximab costs were reimbursed as part of hospital care, thus treatment details were not specified in healthcare claims before 2012. As of 2012, infliximab costs are directly reclaimed by pharmacies based on specific dosages and dispensation dates.

Comorbidity: documented healthcare claims for psoriatic arthritis, ankylosing spondylitis, psoriasis and rheumatoid arthritis.

Outcomes
The primary outcome was anti-TNF drug survival (i.e. time from start of anti-TNF therapy to discontinuation). Secondary outcomes included time to anti-TNF dose intensification, time to corticosteroid initiation and time to IBD-related hospitalisation in anti-TNF starters and analysis of potential determinants for time to drug discontinuation, treatment intensification, hospitalisation, and corticosteroid initiation. Moreover, treatment intervals, dosing regimens and drug costs of anti-TNF therapy were analysed.

Classifications, definitions, calculations and selection criteria
All analyses were performed on patients aged ≥ 18 years at the end of the observation period. Patients who received their first infliximab infusion > 16 weeks after the start of the observation period were considered to be infliximab starters. Patients who received their first pharmacy dispensation of adalimumab > 6 months after start of the observation period were considered adalimumab starters. These cut-offs were based on the assumption that infliximab intervals are unlikely to exceed a 16-week period and that the amount of dispensed adalimumab vials is unlikely to cover a treatment period longer than 6 months. In order to distinguish between patients starting on anti-TNF monotherapy or combination therapy, pharmacy dispensations of immunomodulators and anti-TNF agents were divided into semesters. Anti-TNF starters receiving a prescription for an immunomodulator in the first semester of anti-TNF treatment were defined as patients using combination therapy.

Bots et al. Patterns of anti-TNF use in IBD.

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An infliximab dose adaptation was defined as a dose increase or decrease of at least 30 mg and/or an increase or decrease in the treatment interval between two infusions of ≥ 25%. Infliximab discontinuation was defined as a definite treatment stop or an infusion interval of >16 weeks. Infliximab restart was defined as at least one infliximab infusion after treatment discontinuation.

Adalimumab dosing regimens were based on the average amount of adalimumab provided at each dispensation (amount dispensed in mg divided by the time until next dispensation). Adalimumab dosing regimens were categorised into < 40 mg every other week, 40 mg every other week, 40 mg every week and > 40 mg every week based on the following cut-offs: < 15 mg per week, 15-30 mg per week, 30-60 mg per week and > 60 mg per week, respectively. Adalimumab dose adaptations were defined as a change in dosing regimen category that was maintained for at least two consecutive dispensations. Adalimumab discontinuation was defined as a definite treatment stop or when the average amount of adalimumab that was dispensed by the pharmacy was < 10 mg per week. Adalimumab restart was defined as at least one adalimumab dispensation after discontinuation.

Time to drug discontinuation, treatment intensification, hospitalisation, out of hospital and in-hospital corticosteroid initiation (prednisone and budesonides) were analysed in all patients who started on anti-TNF therapy within the observation period. For all survival analyses, patients were censored on 31 December 2014, at time of death or at the time of an interruption of the insured period (i.e. if patients switched to another health insurance provider). In order to analyse time to corticosteroid initiation, hospitalisation and treatment intensification, patients were also censored at the time of anti-TNF discontinuation.

Corticosteroid use during anti-TNF induction therapy (4 weeks for adalimumab and 6 weeks for infliximab) was used as a cut-off point for analysing time to corticosteroid initiation. Because the definitions of infliximab and adalimumab treatment intensification were not comparable, time to treatment intensification was analysed for both agents separately.

Average anti-TNF treatment intervals and dosages were determined in patients who started on anti-TNF treatment during the observation period at 3, 6, 12 and 24 months after treatment initiation if they were not censored and still receiving the same anti-TNF agent. Mean infliximab dose relative to body weight was estimated using an average body weight of Dutch men and women of 70 kilogram. Drug costs of each anti-TNF dispensation were provided by Achmea. Total anti-TNF costs were calculated as the sum of all dispensions within the observation period and for each year separately.

**Statistical analysis**

All analyses were performed using SPSS 23.0 (IBM, Chicago, Illinois). Descriptive statistics were used to study cohort characteristics. Observed periods are presented in person-years. Comparisons between groups of not normally distributed dichotomous data were performed using Fisher’s exact tests. Survival data are presented as Kaplan-Meier curves. Univariate and multivariate analysis of time to event data was performed using Cox proportional hazards regression. The proportional hazards assumption was tested using visual inspection of log minus log survival plots. The threshold for statistical significance was set at p < 0.05.

**Ethical approval**

All provided data were completely anonymised. Data were requested and obtained through official procedures. Therefore, no ethical approval was required.

**RESULTS**

**Cohort characteristics**

A total of 22,082 patients who received IBD-related care between 2008 and 2014 were identified. The total observation period comprised 131,134 person-years. Cohort characteristics are provided in Table 1. From 2008 to 2014, 1498 patients were treated with adalimumab, and 1671 patients were treated with infliximab between 2012 and 2014. The proportion of patients receiving anti-TNF treatment increased from 17% in 2012 to 19.7% in 2014 (infliximab and adalimumab combined). In this period, 476 out of 2929 (16.3%) patients had received both infliximab and adalimumab. From 2008 to 2014, 24% of IBD patients receiving an anti-TNF agent also received care (indicated by a documented health insurance claim) for at least one other disease for which anti-TNF agents are indicated, such as psoriatic arthritis, ankylosing spondylitis, psoriasis or rheumatoid arthritis.

**Anti-TNF use**

**Infliximab**

Of the patients receiving IBD-related care, the proportion that were treated with infliximab increased from 10.3% in 2012 to 11.3% in 2014. In these patients, yearly drug costs of infliximab treatment were €17.4 million in 2012, increasing to €19.7 million in 2014. At the start of infliximab therapy, the proportion of patients receiving combination therapy was 60.4%, of whom the vast majority received azathioprine (66.5%) or 6-mercaptopurine (26.6%). The proportion of patients receiving combination therapy was comparable in 2012 (59.0%), 2013 (61.0%) and 2014 (61.4%).
During the observation period, 20,252 infliximab infusions were administered. In total 855 patients (550 Crohn’s disease, 305 ulcerative colitis) started on infliximab within the observation period. The distribution of infliximab administration intervals in these patients over time is shown in figure 1. The proportion of patients receiving infliximab maintenance treatment with an infusion interval between 7 and 9 weeks decreased with longer treatment duration (treatment interval between 7 and 9 weeks at 3 months vs. 24 months: 72.3% vs. 60.9%, p = 0.02). The proportion of patients receiving infliximab with an infusion interval shorter than 7 weeks increased with longer treatment duration (treatment interval < 7 weeks at 3 months vs. 24 months: 22.2% vs. 33.6%, p = 0.01). No clinical factors were significantly associated with time to infliximab intensification (i.e. decreased infusion intervals) in univariable and multivariable analysis (table 2). No change in mean infliximab dose per kg bodyweight was observed over time (3 months vs. 24 months: 5.8 [SD 1.8] vs. 5.7 [SD 2.1], p = 0.64).

Adalimumab
Of patients receiving IBD-related care, the proportion who were treated with adalimumab increased from 3.2% in 2008 to 8.4% in 2014. From 2008 to 2014, 121,406 adalimumab syringes were dispensed with a median of 60 (IQR 28 - 118) syringes per patient. Yearly drug costs of adalimumab treatment increased from €3.2 million in 2008 to €13 million in 2014. At the start of adalimumab treatment, the proportion of patients receiving combination therapy was 52.5%, of whom the vast majority received azathioprine (64.4%) or 6-mercaptopurine (18.1%). The proportion of patients starting adalimumab combined with an immunomodulator increased from 42.1% to 51.5% between 2008 and 2014.

A total of 1199 subjects (940 Crohn’s disease, 259 ulcerative colitis) started on adalimumab treatment within the observation period. The distribution of adalimumab administration intervals among these subjects over time is shown in figure 2. The proportion of patients receiving 40 mg adalimumab every other week decreased with

<table>
<thead>
<tr>
<th>Table 1. Cohort characteristics</th>
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<tbody>
<tr>
<td>2008</td>
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</tr>
<tr>
<td>Number of insured patients</td>
</tr>
<tr>
<td>Number of patients receiving IBD-related care</td>
</tr>
<tr>
<td>CD (n, %)*</td>
</tr>
<tr>
<td>UC (n, %)*</td>
</tr>
<tr>
<td>Agea (mean, SD)</td>
</tr>
<tr>
<td>Males (n, %)*</td>
</tr>
<tr>
<td>Deceased (n, %)*</td>
</tr>
<tr>
<td>Receiving infliximab (n, %)*</td>
</tr>
<tr>
<td>• CD (n, %†)</td>
</tr>
<tr>
<td>• UC (n, %‡)</td>
</tr>
<tr>
<td>Receiving adalimumab (n, %)*</td>
</tr>
<tr>
<td>• CD (n, %†)</td>
</tr>
<tr>
<td>• UC (n, %‡)</td>
</tr>
</tbody>
</table>

*a of patients receiving IBD-related care; † of CD patients; ‡ of UC patients. IBD = inflammatory bowel disease; CD = Crohn’s disease; UC = ulcerative colitis; NA = data not available.
longer treatment duration (at 3 months vs. 24 months: 81.5% vs. 71.2%, \( p < 0.001 \)), whereas the proportion of patients who received intensified adalimumab treatment (i.e. \( \geq 40 \text{ mg every week} \)) increased with longer treatment duration (at 3 months vs. 24 months: 10.5% vs. 19.3%, \( p < 0.001 \)). No clinical factors were significantly associated with time to adalimumab intensification in univariable and multivariable analysis (table 2).

**Drug survival**

Median time to anti-TNF treatment discontinuation was 600 days (IQR 156-1693 days). At 6, 12 and 24 months after initiation of anti-TNF treatment, the proportion of patients receiving continuous treatment with anti-TNF agents was 72.5% (95% CI 70.5-74.5), 61.5% (95% CI 59.1-63.9) and 45.6% (95% CI 43.1-48.1), respectively. Univariable and multivariable analysis of factors associated with time to drug discontinuation are shown in table 3. Patients with Crohn’s disease were less likely to stop anti-TNF treatment compared with ulcerative colitis patients (hazard ratio [HR] 0.79 [95% CI 0.69-0.91], \( p = 0.001 \)). Patients who received anti-TNF treatment intensification were less likely to discontinue their treatment (HR 0.62 [95% CI 0.47-0.82], \( p = 0.001 \)). A trend was observed towards a higher discontinuation rate in patients receiving infliximab compared with adalimumab (HR 1.14 [95% CI 0.99-1.34], \( p = 0.071 \)). Combination treatment at initiation of anti-TNF therapy was not associated with longer drug survival (HR 0.99 [96% CI 0.87-1.11], \( p = 0.571 \)). Kaplan-Meier curves of time to anti-TNF discontinuation are shown in figure 3. The proportion of patients who restarted infliximab or adalimumab treatment within 6 months after discontinuation was 19.2% and 21.4%, respectively.

**Table 2. Univariable and multivariable Cox proportional hazards regression analysis of time to anti-TNF treatment intensification**

<table>
<thead>
<tr>
<th></th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Adalimumab</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn’s disease (vs ulcerative colitis)</td>
<td>0.73 (0.43-1.24)</td>
<td>0.246</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.06 (0.70-1.59)</td>
<td>0.779</td>
</tr>
<tr>
<td>Combination treatment at initiation</td>
<td>1.13 (0.75-1.69)</td>
<td>0.560</td>
</tr>
<tr>
<td><strong>Infliximab</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn’s disease (vs ulcerative colitis)</td>
<td>1.07 (0.72-1.57)</td>
<td>0.746</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.39 (0.96-2.00)</td>
<td>0.081</td>
</tr>
<tr>
<td>Combination treatment at initiation</td>
<td>0.78 (0.54-1.13)</td>
<td>0.192</td>
</tr>
</tbody>
</table>

HR = hazard rate; CI = confidence interval.
The proportion of patients restarting infliximab and adalimumab within 12 months after cessation of anti-TNF therapy was 24.3% and 33.4%, respectively (Appendix figure 1 and 2).

**IBD-related hospitalisation**

Among patients who started on anti-TNF treatment within the observation period, the cumulative proportion of patients hospitalised for IBD-related problems was 9.2% (95% CI 7.8-10.6), 13.7% (95% CI 11.9-15.5) and 19.8% (95% CI 17.3-22.3), at 6, 12 and 24 months, respectively.

**Corticosteroid initiation**

The cumulative proportion of patients receiving corticosteroids after initiation of anti-TNF treatment was 14.4% (95% CI 12.4-16.4), 19.2% (95% CI 16.8-21.6)

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**Table 3. Univariable and multivariable Cox proportional hazards regression analysis of time to drug discontinuation**

<table>
<thead>
<tr>
<th></th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Crohn’s disease (vs ulcerative colitis)</td>
<td>0.79 (0.68-0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.92 (0.81-1.04)</td>
<td>0.173</td>
</tr>
<tr>
<td>Infliximab (vs adalimumab)</td>
<td>1.13 (0.99-1.28)</td>
<td>0.065</td>
</tr>
<tr>
<td>Combination treatment at initiation</td>
<td>1.00 (0.89-1.13)</td>
<td>0.94</td>
</tr>
<tr>
<td>Treatment intensification</td>
<td>0.61 (0.50-0.75)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Figure 3. Kaplan-Meier curves of time to anti-TNF treatment discontinuation: a) Crohn’s disease vs. ulcerative colitis; b) adalimumab vs. infliximab; c) standard treatment vs. intensified treatment**

Univariable and multivariable analysis of factors associated with time to hospitalisation is provided in table 4. Crohn’s disease was the only factor that was significantly associated with hospitalisation (HR 1.49 [95% CI 1.10-2.03], p = 0.011). A Kaplan-Meier plot of time to hospitalisation is shown in figure 4.
and 27.2% (95%CI 24.1-30.3) at 6, 12 and 24 months, respectively. Univariable and multivariable analysis of factors associated with time to corticosteroid initiation is provided in Table 5. Patients with Crohn’s disease (HR 0.57 [95% CI 0.45-0.73] p < 0.001) and patients receiving infliximab (HR 0.55 [95% CI 0.42-0.72] p < 0.001) were less likely to receive treatment with corticosteroids. Patients who received combination therapy at the time of initiation of anti-TNF treatment used significantly less corticosteroids as compared with patients receiving anti-TNF monotherapy (HR 0.80 [95% CI 0.64-1.00] p = 0.048). Kaplan-Meier plots of time to corticosteroid initiation are depicted in Figure 5.

**Table 4. Univariable and multivariable Cox proportional hazards regression analysis of time to hospitalisation**

<table>
<thead>
<tr>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Crohn’s disease (vs ulcerative colitis)</td>
<td>1.46 (1.08-1.98)</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.972 (0.77-1.23)</td>
</tr>
<tr>
<td>Infliximab (vs adalimumab)</td>
<td>1.04 (0.82-1.33)</td>
</tr>
<tr>
<td>Combination treatment at initiation</td>
<td>0.83 (0.66-1.05)</td>
</tr>
<tr>
<td>Treatment intensification</td>
<td>1.26 (0.92-1.72)</td>
</tr>
</tbody>
</table>

HR = hazard rate; CI = confidence interval.

**Figure 4. Kaplan-Meier curves of time to hospitalisation: Crohn’s disease vs. ulcerative colitis**

**Table 5. Univariable and multivariable Cox proportional hazards regression analysis of time to corticosteroid initiation**

<table>
<thead>
<tr>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Crohn’s disease (vs ulcerative colitis)</td>
<td>0.61 (0.48-0.77)</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.15 (0.92-1.44)</td>
</tr>
<tr>
<td>Infliximab (vs adalimumab)</td>
<td>0.59 (0.45-0.76)</td>
</tr>
<tr>
<td>Combination treatment at initiation</td>
<td>0.67 (0.51-0.87)</td>
</tr>
<tr>
<td>Treatment intensification</td>
<td>1.07 (0.78-1.46)</td>
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HR = hazard rate; CI = confidence interval.
Anti-TNF discontinuation rates range from 5% to 23% at 12 months of follow-up according to different studies. There are several potential explanations for these differences. Firstly, most of these studies concern analyses of clinical trials and tertiary care cohorts, which may not provide reliable estimates of real-life drug survival. Furthermore, early discontinuation (due to primary non-response or intolerance) may not have been included in these estimates. On the other hand, we may have overestimated the discontinuation rate due to the definitions that were applied. These definitions could not account for poor treatment adherence, short drug holidays or episodic treatment strategies. This may also have contributed to a higher proportion of patients restarting the same anti-TNF agent within 12 months (24% and 33% for infliximab and adalimumab, respectively). However, we presume that the number of patients receiving episodic treatment with TNF blockers is very low in this cohort, since it is well known that scheduled continuous treatment is the preferred treatment strategy.

Strikingly, immunomodulator use at the start of anti-TNF treatment was not associated with a longer drug survival or time to anti-TNF intensification. This is an unexpected finding because combination therapy appears to be more effective than either therapeutic agent alone, explained by reduced immunogenicity, increased anti-TNF serum levels and possible synergistic effects. Nevertheless, several previous studies also found no significant association between time to anti-TNF intensification and concomitant immunomodulator use. We hypothesise that patients with more severe disease are more likely to receive combination therapy. Consequently, the potential beneficial effect of combination therapy may be neutralised by patients’ poorer prognosis. Furthermore, some patients in our cohort could have been misclassified as patients who started on combination therapy. We defined combination therapy at the time of anti-TNF initiation as a pharmacy dispensation of an immunomodulator in the same semester as the first anti-TNF administration. As a result, some patients may have already discontinued the immunomodulator prior to anti-TNF initiation. However, we did find a significantly longer time to corticosteroid initiation in patients on combination therapy as compared with anti-TNF monotherapy, which reflects the beneficial effect of concomitant immunomodulator use.

A diagnosis of ulcerative colitis was associated with a shorter time to anti-TNF discontinuation and corticosteroid initiation. This could reflect lower response rates to anti-TNF agents in ulcerative colitis compared with Crohn’s disease patients. Although head-to-head studies are lacking, it has been suggested that anti-TNF agents may be more effective in Crohn’s disease as compared with ulcerative colitis. In line with this notion, previous
studies have found higher rates of anti-TNF treatment intensification in ulcerative colitis compared with Crohn’s disease patients. A possible explanation for this difference is a higher inflammatory burden and a higher drug clearance in ulcerative colitis patients. However, we did not find a significant association between time to treatment intensification and a diagnosis of ulcerative colitis. Furthermore, other studies found no difference in time to infliximab discontinuation between Crohn's disease and ulcerative colitis. It is currently unclear if infliximab or adalimumab is superior for the treatment of IBD because head-to-head studies are lacking. Results from meta-analyses and several studies show conflicting results. A population study in IBD patients showed no difference in efficacy between these two agents. In our study, infliximab use was associated with a reduced risk of corticosteroid initiation compared with adalimumab. However, the difference in cut-off point between adalimumab and infliximab that we used for time to corticosteroid initiation (an induction period of 4 and 6 weeks, respectively) might have influenced the results. Nevertheless, this finding has also been reported previously in another administrative claims database study that consisted of 1,400 ulcerative colitis patients starting anti-TNF therapy. Furthermore, no difference in time to hospitalisation was found, and a trend towards a higher drug discontinuation rate was seen in infliximab users compared with adalimumab. We postulate that the small difference in discontinuation rate could be explained by the fact that IBD patients with severe disease requiring hospitalisation are more likely to receive treatment with infliximab. Disease severity at the start of anti-TNF treatment could not be assessed in our database, which can cause potential bias for the comparison of the two agents. Hence, based on our results we cannot draw firm conclusions with regard to differences in therapeutic efficacy between infliximab and adalimumab. An ongoing study will determine if higher induction and maintenance doses of adalimumab will improve the outcome in ulcerative colitis patients.

The present study cohort is a representative sample of the Dutch IBD population, consisting of both second and third line patients. More than 22,000 IBD patients receiving IBD-related care between 2008 and 2014 were included. Long-term data from large population-based cohorts allow for robust analyses of patterns of drug use. However, this study has several limitations. Firstly, adalimumab use was based on the amount of drug that was dispensed by pharmacists to patients. Therefore, actual drug use, premature drug discontinuation, therapeutic compliance and variation in drug dispensing rates because of logistical reasons (such as lost drug could not be assessed. Secondly, the definitions that were used for patient selection and classification (such as selection of anti-TNF starters, anti-TNF discontinuation, combination therapy, treatment intensification and corticosteroid initiation) may have resulted in selection bias. Thirdly, relevant clinical information such as disease location, behaviour and severity or reasons for anti-TNF discontinuation and corticosteroid initiation could not be obtained. In addition, surgical interventions could not be evaluated since detailed data on IBD-related surgery were not available. Furthermore, the Dutch health insurance claims system does not allow for a diagnosis of unspecified IBD. Consequently, all IBD cases were categorised as either Crohn’s disease or ulcerative colitis, while approximately 8% of the Dutch IBD population is diagnosed with unspecified IBD. Despite these limitations, this study contributes to the knowledge on the use of anti-TNF agents and is the first to describe patterns of anti-TNF use in a large real-life population in the Netherlands.

CONCLUSION

The proportion of IBD patients receiving anti-TNF treatment increased to almost 20% in 2014, which is a major cost driver. Discontinuation of anti-TNF agents appears to occur earlier than previously reported, which was associated with a diagnosis of ulcerative colitis and non-intensified anti-TNF treatment regimens, but not with combination therapy. However, immunomodulator use at the start of anti-TNF treatment was associated with a longer time to corticosteroid initiation.

ACKNOWLEDGEMENTS

We thank Hugo Smeets and Anne Hollinga from Achmea healthcare for providing us with the database.

Conference presentations

Part of this work was presented at: Digestive Disease Week 2016, San Diego; ECCO congress 2016, Amsterdam; UEGW 2016, Vienna; ECCO Congress 2017, Barcelona; Digestive Disease Week 2017, Chicago.

DISCLOSURES

S.J.A Bots has served as speaker for Abbvie, Merck, Sharp & Dome, Takeda, Jansen Cilag, Pfizer and Tillots.

C.Y. Ponsioen has served as advisor for Abbvie, Takeda; has received research grants from Takeda; has received speaker’s fees from Abbvie, Takeda, and Dr. Falk Pharma
Grants support: No external funding was obtained.

The other authors have no potential conflicts of interest to report.

References


APPENDIX

Appendix figure 1. Time to restart of adalimumab after discontinuation

Appendix figure 2. Time to restart of infliximab after discontinuation
The added value of clinical geriatric assessment prior to geriatric rehabilitation

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'Department of Geriatric Medicine, Tergooi Hospital, Blaricum, the Netherlands, 'University Medical Centre Utrecht, Utrecht, the Netherlands, *corresponding author: email: ngoospeek@tergooi.nl

ABSTRACT

Background: Community dwelling elderly who are temporarily unable to live independently due to functional decline can be referred for geriatric rehabilitation care at a nursing home. This referral is always preceded by a comprehensive geriatric assessment (CGA) by a geriatrician in hospital to rule out an indication for clinical admission and to evaluate geriatric multimorbidity. Because there is little evidence of the effectiveness of this procedure, we aimed to evaluate the results of this assessment and to elaborate on its relevance.

Methods: All patients who were referred by their general practitioner for a CGA in our hospital prior to geriatric rehabilitation care between March and December 2016 were included prospectively. Data were analysed retrospectively. Our primary aim was to describe the percentage of patients with an indication for hospital admission. Other outcomes included new diagnostic findings from the geriatric assessment and recommendations given to the elderly care physician in the geriatric rehabilitation facility.

Results: Of the 32 assessed patients, 25% required admission to hospital, either due to somatic illness, mainly infections or suspected neurological disorders, needing clinical treatment, or for further diagnostics. New findings by geriatric assessment mostly concerned vitamin deficiency and infection, for which treatment recommendations were given to the elderly care physician in the geriatric rehabilitation facility.

Conclusion: Geriatric assessment prior to geriatric rehabilitation referral is essential as it identifies patients needing hospital care, which cannot be provided at a nursing home. Furthermore, the assessment results in important recommendations to the elderly care physician in the geriatric rehabilitation facility.

KEYWORDS

Elderly, geriatric assessment, rehabilitation, geriatrician

INTRODUCTION

Geriatric rehabilitation care is provided at nursing homes for older persons who temporarily suffer from functional decline due to a variety of medical reasons, with the intention to return to independent living after recuperation. It comprises an active form of care, offered on specifically equipped wards by a multidisciplinary team. Originally, geriatric rehabilitation care was provided under the Exceptional Medical Expenses Act (AWBZ). However, as this type of multidisciplinary care is more complex and expensive than long-term nursing care, the financing from the AWBZ was insufficient. Moreover, it did not stimulate short and intensive rehabilitation treatment enough due to fixed day tariffs. Therefore GR care was transferred to the Dutch Health Care Insurance Act (ZVW) in 2013. With this change in funding, hospital admission prior to geriatric rehabilitation became a prerequisite in order to recognise and treat all medical conditions needing hospital care. Consequently, this led to unnecessary clinical admissions as not all patients needed hospitalisation. In 2014 this practice changed and a hospital admission was no longer a precondition. Nevertheless, as advocated by the Dutch Society of Geriatricians (NVKG), a comprehensive geriatric assessment (CGA) performed by a geriatrician prior to geriatric rehabilitation care, to rule out somatic pathology requiring clinical admission and to evaluate geriatric multimorbidity, remained obligatory.
This assessment is incorporated in our regional protocol as an essential precondition before referral for geriatric rehabilitation. The GPs, elderly care physicians and geriatricians in our region are familiar with this arrangement. Thus, the elderly care physicians do not accept patients for admission to a geriatric rehabilitation facility without prior geriatric assessment. Geriatricians perform the assessment on the emergency ward in our general hospital. There is little evidence on the usefulness of this assessment. It may be an unnecessary effort as GP referral directly to geriatric rehabilitation might suffice. The current study aims to provide insight into this trajectory, by evaluating community dwelling patients referred to our hospital by their GP for geriatric assessment prior to geriatric rehabilitation care. The primary aim is to present the percentage of patients admitted to hospital after CGA, as this shows the number of patients actually needing admission into a care facility instead of a care facility. Furthermore, the reason for hospital admission, length of stay, new diagnostic findings and advice given to the elderly care physician are described.

M A T E R I A L S  A N D  M E T H O D S

Study design and population
All community dwelling patients referred by their GP to our emergency ward for geriatric assessment before geriatric rehabilitation referral were included in a period of 10 months. Prior to this, the GP already consulted the elderly care physician, who agreed on geriatric rehabilitation care, providing there is no hospital indication, and arranged a bed on a geriatric rehabilitation ward in a nursing home. A CGA is performed in the emergency room by a geriatrician, and depending on the results the patients will go to the nursing home or will be admitted.

Comprehensive geriatric assessment
A CGA has proven to effectively explore the multiple domains of health in elderly patients in many different clinical settings, among which the emergency department. It is a diagnostic process, which is used regularly by geriatricians to determine medical, functional, psychological and social capabilities and problems of their patients. All patients underwent a standard diagnostic work up in accordance with the guideline ‘Comprehensive Geriatric Assessment’ by the NVKG. It includes a medication review, laboratory tests and relevant diagnostic imaging.

Data collection
For this descriptive study, patients were included consecutively and prospectively between March and December 2016. There were no exclusion criteria. Data were analysed retrospectively. Information of the patient’s status at the moment of presentation was gathered from the patient file, which comprises reason for referral; Charlson Comorbidity Index; cognitive impairment; polypharmacy, defined as chronic use of five or more medications; hearing and visual impairment; activities of daily living (ADL) and instrumental activities of daily living (IADL) dependency and living situation. Data collection was carried out in Castor EDC, a data format which guaranteed anonymity of the patients. The protocol for this study was evaluated and approved by the local ethics committee of the participating hospital.

Endpoints
The primary aim was to determine the percentage of patients that required clinical admission after CGA. We additionally described the reason for hospital admission and length of stay. Furthermore, we collected new diagnostic findings based on the CGA; advice given by the geriatrician to the elderly care physician in the geriatric rehabilitation facility and the rate of admissions to hospital within two weeks after referral for geriatric rehabilitation. Several outcomes were categorised in general groups by three independent researchers; any disagreements were solved by discussion.

Data analysis
Analysis to describe the patient characteristics was performed using SPSS software (version 22). Continuous variables that were distributed normally were displayed using mean and standard deviation. If variables were not normally distributed, the median and IQR were calculated. Categorical variables were displayed with percentages and absolute frequencies. Data were split to visualise the differences between the group with an indication for geriatric rehabilitation care and the group with a clinical admission indication.

R E S U L T S

Patient inclusion and characteristics
In total, 32 patients were included (figure 1). Table 1 presents the characteristics of patients with an indication for geriatric rehabilitation care and patients who had a hospital admission indication after CGA. Mean age was 81.3 years (SD 10.2) vs. 81.8 years (SD 6.8) for the geriatric rehabilitation and hospital indication groups, respectively.

Endpoints
The primary aim was to determine the percentage of patients that required clinical admission after CGA. We additionally described the reason for hospital admission and length of stay. Furthermore, we collected new diagnostic findings based on the CGA; advice given by the geriatrician to the elderly care physician in the geriatric rehabilitation facility and the rate of admissions to hospital within two weeks after referral for geriatric rehabilitation. Several outcomes were categorised in general groups by three independent researchers; any disagreements were solved by discussion.

Data analysis
Analysis to describe the patient characteristics was performed using SPSS software (version 22). Continuous variables that were distributed normally were displayed using mean and standard deviation. If variables were not normally distributed, the median and IQR were calculated. Categorical variables were displayed with percentages and absolute frequencies. Data were split to visualise the differences between the group with an indication for geriatric rehabilitation care and the group with a clinical admission indication.

R E S U L T S

Patient inclusion and characteristics
In total, 32 patients were included (figure 1). Table 1 presents the characteristics of patients with an indication for geriatric rehabilitation care and patients who had a hospital admission indication after CGA. Mean age was 81.3 years (SD 10.2) vs. 81.8 years (SD 6.8) for the geriatric rehabilitation and hospital indication groups, respectively. There was a high rate of polypharmacy in both groups at 75.0%. In the geriatric rehabilitation indication group, a higher rate of visual impairment was seen. The majority of both groups received informal care. More patients in the hospital indication group were ADL- and IADL-dependent and received home care. All patients were referred by their GP because of functional decline, primarily due to...
a fall-related injury, mostly concerning suspicion of hip contusion and backache.

Findings
As shown in figure 1, of all the 32 patients, eight (25.0 %) had an indication for clinical admission. Table 2 shows that six patients required medical treatment, primarily for a respiratory infection or a complicated urinary tract infection. Two needed further diagnostics for suspected neurological disorders, concerning possible cauda equina syndrome and lumbar spinal stenosis. Their average stay was 5.7 days, with a range of one to 12 days. After hospital stay seven patients went to a GR facility, one patient moved to a long-term care facility for elderly with dementia.

Table 1. Baseline characteristics of participants allocated by admission indication

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>GR indication (n = 24)</th>
<th>Hospital indication (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>81.3 (10.2)</td>
<td>81.8 (6.8)</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>20 (83.3)</td>
<td>4 (50.0)</td>
</tr>
<tr>
<td>Somatic status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>18 (75.0)</td>
<td>6 (75.0)</td>
</tr>
<tr>
<td>Incontinence</td>
<td>10 (41.7)</td>
<td>4 (50.0)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index, median (IQR)</td>
<td>1.5 (1.0)</td>
<td>1.0 (0.5)</td>
</tr>
<tr>
<td>Psychological status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitively impairedd</td>
<td>2 (8.3)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Functional status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing impairmente</td>
<td>7 (29.2)</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td>Visual impairmentf</td>
<td>10 (41.7)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>ADL independentg</td>
<td>9 (37.5)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>IADL independenth</td>
<td>8 (33.3)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Social status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living single</td>
<td>20 (83.3)</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>Home care</td>
<td>16 (66.7)</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>Informal care</td>
<td>18 (75.0)</td>
<td>6 (75.0)</td>
</tr>
<tr>
<td>Reason for referral to GR (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional decline due to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall related injury</td>
<td>13 (54.1)</td>
<td>5 (62.5)</td>
</tr>
<tr>
<td>Somatic disease</td>
<td>9 (37.5)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>Unknown origin</td>
<td>2 (8.3)</td>
<td>1 (12.5)</td>
</tr>
</tbody>
</table>

Values are numbers (percentages) unless stated otherwise. a Five or more chronically used medications on ATC3 level.13 b Partial or total incontinence of bowel and/or bladder. c Score range of 0 to 31, with a higher score indicating more (severe) comorbidity. d Outcome based upon (1) dementia mentioned in medical history and/or (2) information gathered on emergency department. e Use of hearing aids counts as an impairment. f Visual impairment, regardless of use of glasses. g Activities of Daily Living. h Instrumental Activities of Daily Living. i Help with ADL/IADL, domestic work not included. GR = geriatric rehabilitation.

Goos-Peek et al. Geriatric Assessment prior to Geriatric Rehabilitation.
Twenty-four patients had a geriatric rehabilitation indication, of which 21 went directly to a geriatric rehabilitation facility. One patient went home, because he refused rehabilitation. Two patients stayed in hospital for one night because no bed was available in the geriatric rehabilitation facility (figure 1).

New diagnostic findings after CGA mainly included infection (four patients with urinary tract infection and two patients with respiratory infection) and fall-related fractures, including vertebral, costal and femur fractures.

In the geriatric rehabilitation indication group, the advice given to the elderly care physician concerned management of somatic problems in 75% of cases, e.g. vitamin supplements or treatment of infection or osteoporosis, and often on pain management and drug dosage adjustment. None of the 24 patients with an indication for geriatric rehabilitation were readmitted to the emergency department within two weeks after referral to the rehabilitation facility.

**DISCUSSION**

We studied the added value of a geriatric assessment in hospital prior to geriatric rehabilitation care. The main finding is that a fourth of all patients referred by their GP for geriatric rehabilitation required hospital admission. Thus, geriatric evaluation prior to referral for geriatric rehabilitation is essential to rule out the need for hospital care. Next, our study shows that the assessment results in important diagnostic findings and useful recommendations for the elderly care physician in the geriatric rehabilitation facility, mostly concerning somatic problems and medication adjustments.

As this specific trajectory to geriatric rehabilitation is based on national legislation, our results cannot be compared with international findings. Also, as far as we know, no previous evaluations in the Netherlands have taken place on this specific issue, namely the community dwelling patients referred by their GP. However, our findings are in line with the expectations of the NVKG, who stated that this geriatric evaluation is necessary to select patients in need of clinical care.

As the assessment is performed in hospital, extensive and faster options for diagnostics are available compared with an evaluation in a care facility. It results in appropriate clinical treatment for patients with underlying acute illness. Admission to a care facility will, in all likelihood, cause a delay in treatment. Moreover, none of the patients were readmitted to hospital after referral to a geriatric rehabilitation care facility, which is consistent with prior studies in which a geriatric assessment adequately selects patients with a high risk of readmission. In two cases direct admission for rehabilitation care was not possible because no beds were available in a geriatric rehabilitation facility. It shows that beds are sometimes available to a limited extent resulting in unnecessary hospital admissions, which leads to additional healthcare costs.

A major strength of the study is that a fixed regional protocol was used to select and refer community dwelling patients to geriatric rehabilitation care, which enabled us

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**Table 2. Secondary outcomes**

<table>
<thead>
<tr>
<th>Reason for hospital admission (%)</th>
<th>n = 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical treatment required</td>
<td>6 (75.0)</td>
</tr>
<tr>
<td>Further diagnostics required</td>
<td>2 (25.0)</td>
</tr>
</tbody>
</table>

| Length of stay days, mean (min; max) | 5.7 (1;12) |

<table>
<thead>
<tr>
<th>Most frequent new findings after CGA (%)</th>
<th>n = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiency</td>
<td>11 (34.4)</td>
</tr>
<tr>
<td>Infection</td>
<td>6 (18.8)</td>
</tr>
<tr>
<td>Fall-related fracture(s)</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>(Suspected) neurological disorder</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>Adverse drug reaction</td>
<td>3 (9.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most given advice to elderly care physician in GR facility (%)</th>
<th>n = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management of somatic problems</td>
<td>18 (75.0)</td>
</tr>
<tr>
<td>Pain management</td>
<td>10 (41.7)</td>
</tr>
<tr>
<td>Drug dose adjustment</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Management of psychiatric problems</td>
<td>4 (16.7)</td>
</tr>
</tbody>
</table>

Values are numbers (percentages) unless stated otherwise. *Multiple options per patient possible. GR = geriatric rehabilitation.
to include all patients of our region in the study period. The present study also has some limitations. It has a rather small sample size and a relatively short study duration. Next, the study was performed in one hospital, thus one region. It is possible that there are interregional differences arising from a different interpretation of legislation, resulting in a slightly different care trajectory.

**CONCLUSION**

This study shows that current practice is effective. Geriatric assessment prior to geriatric rehabilitation care referral is essential to rule out the need for hospital admission. Also, it results in new diagnosis and relevant recommendations for the elderly care physician in the geriatric rehabilitation facility.

**DISCLOSURES**

All authors declare no conflict of interest. No funding or financial support was received.

**REFERENCES**

CASE REPORT

‘Khatatonia’ – cathinone-induced hypertensive encephalopathy

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ABSTRACT

Khat consumption is an under-recognised cause of hypertensive encephalopathy and intraparenchymal brain haemorrhage. We report the radiological findings of extensive periventricular, subcortical and brain stem white matter pathology of a patient who had consumed excessive amounts of Khat. The Khat plant contains cathinone, an amphetamine-like alkaloid which has been associated with chronic hypertensive end-organ damage, but is seldom considered a cause of cerebrovascular events in northern Europe.

KEYWORDS

Neuroimaging, intracerebral haemorrhage, clinical neurology, MRI, toxicology, stroke

INTRODUCTION

The ethnicity of a patient and cultural factors are rarely the key to the diagnosis in acute neurology. While certain metabolic disorders are associated with ethnic groups, rare neurodegenerative disorders are linked to relatively isolated communities, and multiple sclerosis is associated with geographic latitude, the cultural background of a patient is seldom helpful in neurological emergencies. Haemochromatosis, cystic fibrosis, coeliac disease, and multiple sclerosis are relatively common in Ireland, and many of these conditions have a strikingly low incidence in East-Africa and in the Middle-East. Thalassaemia, Bechet’s disease, and sickle-cell anaemia on the other hand have a low incidence on the island of Ireland. Routine screening in Irish emergency departments reflects the commonest presentations and toxicology tests typically include amphetamines, opiates, paracetamol, benzodiazepines, tricyclic antidepressants, cannabis, and alcohol. Serum and urine toxicology tests are routinely performed in first seizures, unexplained behavioural disturbances, patients with previous self-harm and in other vulnerable patient cohorts. While neurologists worldwide take pride in the fast integration of subtle clinical findings and radiological cues, cultural factors are often overlooked. We present the case of a critically ill young man from Somalia whose radiological presentation was initially a conundrum.

CASE REPORT

A 45-year-old right-handed Somalian man with a background of hypertension and chronic kidney disease, was brought to the hospital with agitation, confusion and severe headaches. His Glasgow Coma Scale score was initially 15/15 and his blood pressure was 220/130 mmHg. Shortly after arrival, he developed a left...
hemiparesis, then a cluster of seizures. He was intubated
and computed tomography of the brain revealed a large
right temporo-parietal intraparenchymal haematoma
with intraventricular extension, a small left parietal
haematoma, and hydrocephalus. Four-vessel digital
subtraction angiography did not identify aneurysms or
arteriovenous malformations, but was suggestive of focal
pericallosal artery constriction, without definite evidence
of vasoconstriction or beading of any other arteries. A left
external ventricular drain was inserted and the neurology
service was consulted. The patient was first assessed
while ventilated and on propofol sedation. His blood
pressure remained 190/100 mmHg despite aggressive
antihypertensive therapy, his fundoscopy showed evidence
of grade III hypertensive retinopathy. He was hyperreflexic
in all four limbs and had absent corneal and vestibulo-
ocular reflexes.

His urgent MRI brain scan revealed confluent pontine,
mesencephalic, thalamic and periventricular white matter
hyperintensities on FLAIR and T2-weighted brain imaging
in addition to the right temporo-parietal haemorrhage
(figure 1). Based on the MRI findings, the differential
diagnosis included hypertensive encephalopathy, posterior
reversible encephalopathy syndrome (PRES), acute toxic
leukoencephalopathy, vasculitis and infective aetiologies,
including fungal and flavivirus infections.

The patient’s renal profile revealed a creatinine of
393 μmol/l and urea of 23.3 mmol/l. The 24-hour urinary
catecholamine and metanephrine levels were normal
and blood film and haematological screens showed no
evidence of thrombocytopenic purpura, haemolytic-
uraemic syndrome, disseminated intravascular coagulation
or microangiopathic haemolytic anaemia. While serum
and urine toxicology were negative for amphetamines
and cocaine metabolites, the constellation of chronic
hypertensive end-organ damage and the acute hypertensive
crisis led to the suspicion that the patient may have
consumed Khat.

Figure 1. FLAIR and T2-weighted brain imaging shows confluent pontine, mesencephalic, thalamic and
periventricular white matter hyperintensities as well as a right temporo-parietal haemorrhage with mass
effect. A left anterior external ventricular drain is in situ. The differential diagnosis included hypertensive
encephalopathy, PRES, acute toxic leukoencephalopathy, vasculitis and infective aetiologies.
DISCUSSION

The leaves of the Khat plant (Catha edulis) contain cathinone, an amphetamine-like alkaloid. Chewing of Khat is uncommon in Ireland, but has a long tradition in Yemen, Ethiopia, Sudan and Somalia. It has been widely used since the 7th century and its cultivation in the region predates coffee production. It has been associated with chronic hypertension, acute hypertensive crisis, psychiatric, cardiac and cerebrovascular events. Our suspicion was corroborated by family members and neighbours who confirmed that the patient had been consuming copious amounts of Khat prior to his admission.

While our patient has survived the acute phase, he acquired considerable long-term deficits. Despite intensive multidisciplinary neurorehabilitation efforts, he has only made limited functional gains. Sadly, he remains essentially non-verbal and unable to mobilise independently. From a radiological perspective, the acute haemorrhages showed gradual resolution, but gliotic changes ensued. The extensive periventricular white matter changes showed only partial improvement. The case showcases a relatively rare cause of toxic leukoencephalopathy. In our view, it also highlights how cultural factors and meticulous history taking may be the key to explaining seemingly disparate clinical cues.

DISCLOSURES

Dr Bede is supported by the Health Research Board (HRB-Ireland; HRB EIA-2017-019), the Irish Institute of Clinical Neuroscience IICN – Novartis Ireland Research Grant, and the Iris O’Brien Foundation. The other authors have no disclosures to report.

REFERENCES

Successful treatment of leptomeningeally metastasised pituitary carcinoma with temozolomide

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ABSTRACT
A 69-year-old man presented with leptomeningeally metastasised pituitary carcinoma, rapidly progressing despite previous treatment with resection, radiotherapy and cabergoline. The patient received temozolomide chemotherapy, resulting in a complete clinical, radiological and biochemical response after 14 cycles, which has been maintained since then. This case lends further support to the role of temozolomide in refractory pituitary tumours.

KEYWORDS
Temozolomide, pituitary carcinoma, prolactinoma

INTRODUCTION
About 15% of all new primary tumours of the brain and central nervous system consist of pituitary adenomas.¹ Pituitary adenomas are classified according to their pattern of hormonal secretion, with prolactinomas and non-functioning pituitary adenomas as the most common subtypes.² Pituitary carcinomas form an extremely rare, aggressive variant of pituitary adenomas which – by definition – involve cerebrospinal and/or systemic metastases and account for 0.1% of the pituitary tumours.³ These tumours have an average survival of less than four years because of a rapid and invasive growth pattern, and relapse frequently despite the current therapies.⁴ Some pituitary tumors exhibit clinically aggressive behavior that is characterized by tumor recurrence and continued progression despite repeated treatments with conventional surgical, radiation and medical therapies. Temozolomide, an alkylating oral chemotherapeutic agent, is widely used to treat glioblastoma.⁵ We present a case of pituitary carcinoma with a dramatic and durable complete response to temozolomide.

CASE REPORT
A 37-year-old man underwent a craniotomy with subtotal resection of a pituitary tumour, which was discovered during evaluation for chronic headaches. Histological examination revealed a prolactinoma and adjuvant radiotherapy, with a total dose of 50 Gy, and suppletion hormonal therapy were administered. Over the next 21 years, follow-up consisted of repeated measurement of the prolactin level and showed stable disease. After those 21 years, elevated prolactin and growth hormone levels (earliest recorded levels: prolactin level 13.50 IU/l (reference values 0.10-0.65) and IGF-1 342 ng/ml (reference values 52-162)) led to MRI scanning showing progression of the residual lesion in the sellar region, suggesting mixed prolactinoma and growth hormone secreting tumour. Therefore the patient was treated with bromocriptine, an oral dopamine D2 receptor antagonist. Because of intolerance, the patient was switched to cabergoline, a long-acting dopamine agonist specific for the D2 receptor, and successfully treated for one year (until 22 years post-surgery). Aged 60 years, 23 years after the initial diagnosis, he underwent surgery for a meningeal tumour at the right jugular foramen which was found on a routine follow-up MRI scan. Histology revealed pituitary adenoma. Since the resection was irradial, the patient underwent local postoperative radiotherapy with a total dose of 50.4 Gy
with leptomeningeal metastases was made based on rapidly progressive symptomatology (motor impairment with increasing fall risk), medical history, radiology and CSF abnormalities, despite the negative CSF cytology. On the advice of the multidisciplinary tumour board, temozolomide chemotherapy 200 mg/m\(^2\)/day days 1-5 every 4 weeks (total dose of 500 mg per day) was started in the absence of feasible local treatment options. After 4 cycles, the patient experienced improvement of his gait. Biochemical and radiological evaluation after 9 cycles revealed partial remission. After 14 cycles normalisation of prolactin levels was reached and maintained since then (figure 2). As the treatment was well tolerated, the patient continued therapy for 21 cycles without dose reductions. Thirty-four years after first presentation, it was decided to discontinue chemotherapy as clinical, biochemical and radiological complete remission was obtained. The most recent neurological, biochemical and radiological evaluation, 34 months after completion of temozolomide, showed continued complete remission. On retrospective tissue review, MLPA analysis of metastasis tissue showed no hypermethylation of O(6)-methylguanine-DNA methyltransferase (MGMT) and normal MLH1, MSH2, MSH6 and PMS2 gene profiling. The fraction of proliferation determent with monoclonal antibody Mib-1, which is comparable with Ki67,\(^2\) was only 5%.

Figure 1. Magnetic resonance imaging of the lumbosacral spine, showing a response to temozolomide (mid-sagittal T1-weighted post-gadolinium images): A) pre-therapy, B) after 6 cycles, C) after 21 cycles. The arrows point to the nodular metastases

Van der Vlist et al. Temozolomide for pituitary carcinoma.
DISCUSSION

In the World Health Organisation (WHO) classification for pituitary tumours of 2004, the term ‘pituitary carcinoma’ is restricted to tumours with proven cerebrospinal and/or systemic metastases. Aggressive pituitary adenoma is used for medical and radiotherapy resistant pituitary lesions. Distinction between pituitary adenoma and carcinoma based on morphology remains challenging. Increased (> 3%) Ki-67 labelling index and p53 immunoreactivity suggest aggressive potential of the tumour or malignant transformation. Nowadays treatment consists of resection, radiotherapy in unresectable or recurrent cases, and dopamine antagonists for prolactinomas. No registered treatment is available for patients in whom these treatments fail. This is most strikingly the case for pituitary carcinomas, since the dissemination in the central nervous system is rarely amenable to resection and craniospinal radiotherapy is associated with considerable toxicity. We found 25 articles in the literature on pituitary carcinomas (n = 79) or treatment-resistant pituitary adenomas that were treated with temozolomide since the first publication in 2006. Clinical efficacy (partial or complete response or stable disease) was observed in 39 cases; a recent review estimated response rates to be 58% in aggressive pituitary adenomas and 55% in pituitary carcinomas. The overall experienced toxicity was mild.

Given the rarity of the diagnosis of pituitary carcinoma, it is unlikely that randomised studies will be performed. The current case with local radiotherapy and dopamine agonist resistant prolactin producing pituitary carcinoma adds to the available literature by underscoring the potential efficacy of temozolomide and good tolerability, even in the setting of biochemically active, symptomatic and widespread leptomeningeal metastases.

Temozolomide has proven efficacy in the treatment of glioblastoma. In these malignant primary brain tumours, hypermethylation of the promoter of MGMT, a gene involved in DNA repair, is predictive of efficacy of temozolomide. MGMT hypermethylation has been found in some pituitary adenomas. In our case, MGMT was not hypermethylated. Although this may be due to imperfections in the currently available MGMT assays, this finding suggests that efficacy of temozolomide cannot be predicted solely on the basis of MGMT status.

CONCLUSION

In this case of pituitary carcinoma with extensive leptomeningeal spread, associated debilitating neurological symptoms, and proven resistance to registered therapies, prolonged treatment with temozolomide led to a complete and durable remission and clinical improvement. These observations lend further support to the role of temozolomide in refractory pituitary tumours.

DISCLOSURES

No grant support needs to be reported. Conflict of interests: none declared.

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Van der Vlist et al. Temozolomide for pituitary carcinoma.
Van der Vlist et al. Temozolomide for pituitary carcinoma.
CASE REPORT

Solitary mediastinal angiomatosis: report of two cases and review of the literature

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ABSTRACT

Angiomatosis is a rare benign vascular lesion, usually seen in females in the first two decades of life. It commonly involves the lower extremities. Angiomatosis of mediastinum is very rare and we report two such cases with a review of the literature on solitary mediastinal angiomatosis.

Both of our patients were female, aged 34 and 57 years. One patient presented with left-sided subcutaneous supraclavicular swelling. Magnetic resonance imaging showed a mass extending from the left upper mediastinum to the left supraclavicular area, measuring 6 cm in the largest diameter. Left thoracotomy was performed which revealed a mass that infiltrated within the pectoral muscle fibres, infiltrating the pericardium and extending behind the left clavicle. The tumour was completely resected. Macroscopic examination revealed a fatty appearing mass with multiple blood vessels and haemorrhagic foci. Histologically, the lesion was composed of mature fat tissue and randomly scattered multiplied, irregular, dilated blood vessels, with thick walls, predominantly of the venous type. Clusters of capillary-sized vessels were adjacent to larger vessels and in their walls. The lesion was deemed to be angiomatosis. The patient was followed up with chest X rays at 1, 3 and 6 months postoperatively. There were no signs of recurrence of the disease 10 months after surgery.

CASE 2

A 57-year-old woman presented with dyspnoea, general weakness and a left-sided pleural effusion of 2 months’ duration. She had a previous history of cholecystectomy, bilateral adnexectomy due to endometriosis and a 10-year history of treated hypertension. Computed tomography of the chest disclosed an infiltrative mass in the mediastinum with the left-sided pleural effusion (figure 1). Video-assisted thoracoscopic surgery was performed in another institution and was unsuccessful. A positron emission tomography-computed tomography scan performed afterwards revealed minimal metabolic activity (maximum standardised uptake value was 2.7). No pathological findings were seen in the regional lymph nodes and the biodistribution of the glucose analogue in the rest of the body was normal. An open thoracotomy was performed during which a mediastinal tumour was found. It extended above the
aortic arch, infiltrating the brachiocephalic vein, and vagal and phrenic nerve. The tumour and infiltrated structures were completely resected. Macroscopic examination showed a yellow mass with multiple blood vessels and poorly defined borders measuring 4 x 3 x 1.5 cm. The lesion was similar to the lesion described in the first case, and diagnosed as angiomatosis. The pleural effusion cyto-analysis showed a lymphocytic type of effusion (80% lymphocytes, 15% mesothelial cells, 5% macrophages) and no trace of malignant cells. Her follow-up was at 1, 3, 6 months postoperatively with no signs of local recurrence on the CT scan 10 months after the operation (figure 2A and B).

**DISCUSSION**

Angiomatosis is a rare benign vascular lesion with extensive and infiltrative growth. It is usually found in the lower extremities, followed by the chest wall, abdomen and upper extremities. Angiomatosis located in the mediastinum is extremely rare, especially when found as a solitary lesion, as in the two cases presented here. It is assumed that angiomatosis has its inception in utero or in the neonatal period given its slow growth. This could explain why angiomatosis usually gives rise to its first symptoms in the first two decades of life.\(^1\) We have shown two rare cases of mediastinal angiomatosis with a late onset in two female patients. Our 57-year-old patient is the second oldest reported patient with newly discovered mediastinal angiomatosis (the oldest reported patient was 63 years old).\(^2\)

On the CT and MRI, angiomatosis shown as a diffuse nonhomogeneous mass can give a mistaken impression of a malignant tumour. Macroscopically seen serpiginous density within this mass (the areas histologically correspond to tortuous vessels) can point to angiomatosis, but the final diagnosis is usually established by histology.\(^3\)

The histological characteristic of angiomatosis is mature fat tissue and large irregular veins along with capillary-sized vessels adjacent to or in their walls,\(^1\) as was found in the cases described here. Angiomatosis is histologically different from infiltrating lipoma, angiolipoma, angiomyolipoma, angiomyxolipoma,
intramuscular angioma and liposarcoma, which can macroscopically look similar.

Patients with mediastinal angiomatosis usually present with symptoms of haemorrhage (haemothorax, haemomediastinum, haemoptysis), local compression (dyspnoea, cough), chest pain and pleural effusion, although sometimes these lesions are incidentally detected. Similarly to those reported symptoms, one of our patients presented with pleural effusion and the other one with neck swelling.

In localised cases of angiomatosis, complete surgical resection is the treatment of choice because of the high tendency for local recurrence. In the study reported by Rao et al., 50% of patients with angiomatosis in various anatomical locations had local recurrences. That is probably due to the incomplete excision of the lesions (according to the authors, 90% of these lesions persisted after surgical excision). In their study, recurrences usually occurred within five years after excision. No data were found specifically for mediastinal angiomatosis. None of the seven cases of mediastinal angiomatosis found in the PubMed search reported recurrence. The longest reported follow-up was 14 months. Hence further, long-term follow-up of patients with mediastinal angiomatosis is necessary.

There are no current guidelines for the treatment of angiomatosis. Though angiomatosis does not show a tendency for malignant alteration, due to its infiltrative and extensive growth, it can cause significant clinical complications. It is important to recognise angiomatosis, treat it with wide surgical excision and monitor with close follow-up.

**DISCLOSURES**

All authors declare no conflict of interest. No funding or financial support was received.

**REFERENCES**


PHOTO QUIZ

Fatal sudden paralysis of the lower extremities

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CASE REPORT

A 34-year-old, otherwise healthy man visited the emergency department with sudden painless paralysis of both legs for the past three days. Apart from trouble with urinating and feeling feverish, he had no other symptoms. When asked, the patient admitted to excessive alcohol and nicotine use of up to 3 litres beer and 6-12 cigarettes a day. He declined using drugs.

On physical examination, an Afro-American male was seen. He had a pulse of 123 beats/min, his blood pressure was 154/108 mmHg. His temperature was 35.7° Celsius, and his SpO2 was 97%. He had a complete paralysis of both his legs, and loss of sensibility. Both his legs were pale and cold. The pulsations of the femoral, popliteal, anterior tibial and dorsalis pedis arteries were absent on both sides. The neurological examination was normal: motoric and sensory function of the cranial nerves was intact, there was no paralysis or loss of sensibility of his upper extremities and the coordination was not impaired. The electrocardiogram (ECG) showed a sinus tachycardia of 130 beats/min, but no other abnormalities. Laboratory tests revealed a slightly elevated leukocyte count of 17.1 (normal value: 4.0-10.0 x 10⁹/l), a C-reactive protein of 94 (CRP: 0-8 mg/l), an elevated lactate dehydrogenase level of 3068 (LDH: 0-248 U/l), a creatinine kinase level of 128,932 (CK: 0-145 U/l), an aspartate transaminase of 2155 (ASAT: 0-31 U/l), and an alanine transaminase of 365 (ALAT: 0-34 U/l). The arterial blood sample was normal with the exception of an elevated lactate of 2.9 (0.5-1.7 mmol/l). His vitamin B1, B6, B12 and his folic acid levels were within the normal range. Lumbar puncture showed a leukocyte count of 1.0 (0.0-5.0 x 10⁹/l), a glucose of 4.2, and an albumin of 115.9 (100-300 mg/l); there were no erythrocytes. Magnetic resonance imaging of the cerebrum, and thoracic and lumbar spine showed no abnormalities. A computed tomography with angiography scan was performed (figure 1).

WHAT IS YOUR DIAGNOSIS?

See page 459 for the answer to this photo quiz.
DIAGNOSIS

The CT scan revealed a large thrombus in the infra-renal abdominal aorta, the iliac arteries and the upper portion of both femoral arteries (figure 1A). Renal and hepatic infarction was seen (figure 1B). Combined with the acute presentation and extreme rhabdomyolysis, indicated by the increased CK, ASAT and LDH levels, the diagnosis of acute aortic occlusion (AAO), also known as Leriche syndrome, was made. Aortic occlusion is an extremely rare disease, only a few hundred cases have been reported in the literature. Chronic aortic occlusion usually presents with slowly progressive and vague symptoms such as erectile dysfunction, hypertension, intermittent claudication and symptoms of arterial insufficiency in the lower extremities or even more subtly with chronic deterioration of kidney function alone. The typical patients are males between 50-70 years with marked atherosclerosis and a history of smoking. In these patients collateral arteries have been formed, explaining the often mild symptoms. The vascular emergency of AAO, however, typically presents with acute and painful cold ischaemia and rhabdomyolysis. A case series from a tertiary hospital, describing 46 consecutive patients with AAO in a period of 40 years, found cardiac embolism to be the cause of AAO in 65%. Atherosclerosis accounted for the remaining 35%. High rates of morbidity and mortality after surgical treatment are described, 74% and 35%, respectively. Recurrent arterial embolism occurred in 43% of the patients with embolic AAO.

In our case, the painless presentation of paralysis and the young age of the patient in the absence of a relevant medical history delayed the correct diagnosis. A broad differential diagnosis, including dry Beriberi, Guillain-Barre, transverse myelitis and polymyositis was made. To exclude these diagnoses, a lumbar puncture was performed, followed by an MRI of the brain and the myelum. It was not until the following morning that a vascular problem was suspected when an ultrasonic arterial Doppler examination showed no arterial pulsations in the femoral arteries, and subsequent CTA of the whole body was carried out, which provided the diagnosis. The patient underwent amputation of both legs combined with aortic thrombectomy to achieve revascularisation: the standard therapy in both acute and chronic Leriche syndrome in the presence of organ or muscular necrosis. His postoperative recovery was complicated by multiple wound infections and decubitus requiring multiple operations and progressive organ failure. The patient opted for euthanasia and received this on the 18th day of admission. Autopsy and hypercoagulability tests, including JAK2 V617F mutation analysis, rotational thromboelastometry, antcardiolipin antibodies, lupus anticoagulants and ANCA, provided no cause for this fulminant presentation. No structural abnormalities of the heart were found.

REFERENCES

PHOTO QUIZ

Air is everywhere

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CASE REPORT

A 71-year-old female presented to the emergency department with bloody diarrhoea and lower abdominal pain. Her past medical history included a hysterectomy and hypertension for which she took bisoprolol and felodipine. She was a non-smoker and did not use any alcohol or illicit drugs. On examination she was in pain. Her vital signs included a temperature of 35.6 °C, blood pressure 149/91 (110) mmHg, pulse rate 75/min and respiration rate 28/min. Oxygen saturation on ambient air was 98%. Physical examination revealed tenderness over the lower abdomen with muscular rigidity. Rectal examination yielded bright red blood with no palpable masses.

The laboratory results showed elevated inflammation parameters (WBC 15.8 x 10⁹/l; CRP 350 mg/l), slightly elevated liver enzymes (ASAT 132 U/l; ALAT 158 U/l; AP 78 U/l; gGT 133 U/l; LDH 844 U/l) and an amylase of 1524 U/l. Arterial blood gas showed a metabolic acidosis with a lactate of 10 mmol/l. The differential diagnosis included pancreatitis, (ischaemic) colitis and perforated diverticulitis. A CT abdomen was subsequently performed.

WHAT IS YOUR DIAGNOSIS?

See page 461 for the answer to this photo quiz.
DIAGNOSIS

The CT abdomen was abnormal with aerobilia, portal venous gas and extensive pneumatosis of a large part of the jejunum. Inflammation of the pancreatic parenchyma and peripancreatic tissues with partial pancreatic parenchymal necrosis was found. There was normal perfusion of the aorta and large abdominal arteries.

In conclusion, this patient suffered from a severe necrotising pancreatitis (APACHE II score 16; CT severity index 10). Due to the extensiveness of the necrosis, surgery was not possible. The patient was treated with broad-spectrum antibiotics and vasopressors on the intensive care unit. Despite this treatment her condition deteriorated quickly and eventually the patient refused any further treatment.

Hepatic portal venous gas in combination with the presence of pneumatosis intestinalis is a severe condition with high mortality rates. It is mostly associated with full-thickness bowel wall necrosis, but also described in other conditions such as necrotising pancreatitis.

REFERENCES

A more restrictive use of quinolones in patients with community acquired pneumonia is urgently needed

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Dear Editor,

Since the extensive Legionella outbreak in Bovenkarspel in 1999, with 188 pneumonia cases and 23 deaths, the prevention and control of Legionella infections have become a national concern.¹ This might have contributed to the current concern for underdiagnosing Legionella pneumonia and thereby the frequent use of ciprofloxacin in the empirical treatment of community acquired pneumonia (CAP).

Annually, about 110,000 cases of CAP are seen in the Netherlands, out of which 15% require hospitalisation.² Publications state that a noteworthy percentage of 1% (ICU) to 6% (non-ICU) of these infections are caused by Legionella spp.³,⁴ This would account for 800 hospitalised patients with Legionella pneumonia per year. However, this number contrasts with the 300-400 Legionella cases which are reported to the National Institute for Public Health each year.³ This is in accordance with a recent Dutch multicentre study of 2283 patients admitted for CAP, which showed an incidence of pneumonia caused by Legionella spp. of less than 1%.⁴ Hence, the incidence of Legionella is probably lower than previously assumed.

In addition, the study by Postma et al. demonstrated that it is safe not to treat Legionella spp. empirically in patients admitted to non-ICU wards. As a consequence, the added value of empirical treatment of Legionella spp. in patients with CAP can be questioned. Unnecessary use of quinolones in the empirical treatment of CAP contributes to avoidable selection pressure on resistant Enterobacteriaceae as well as avoidable side effects directly, or via interaction with co-medication.

Ciprofloxacin in combination with a beta-lactam antibiotic is a frequently prescribed treatment regimen in patients with CAP admitted to our hospital. Therefore, we performed a retrospective cohort study to assess the appropriateness of ciprofloxacin combination therapy in these patients. From the pharmacy database, all patients treated with ciprofloxacin plus beta-lactam antibiotic combination therapy in the Leiden University Medical Centre between June 2015 and June 2016, were identified. From this population we included all patients who were diagnosed with CAP according to the patient medical record. We assessed whether ciprofloxacin was given in accordance with the 2011 CAP-guideline.⁶ We used CURB-65 scores, which are calculated by assigning 1 point per condition for confusion, urea ≥ 7.0 mmol/l, respiratory rate ≥ 30/minute, either a systolic blood pressure ≤ 90 mmHg or a diastolic blood pressure ≤ 60 mmHg, and age ≥ 65 years,⁷ as severity index and checked if Legionella testing had been done. To determine the actual need for ciprofloxacin therapy, we also investigated the incidence of the Legionella pneumonia in our hospital during the studied period.

As shown in table 1, 210 patients were included, out of which only 43% received treatment with ciprofloxacin according to the 2011 Dutch CAP guideline.⁶ While all studied patients received Legionella treatment, only in 139 (66%) tests were performed to detect this pathogen. During the studied period, the causal pathogen was microbiologically proven to be Legionella pneumophila in five of the 210 CAP cases. This number corresponds with the total number of five Legionella pneumophila cases in our hospital from June 2015 to June 2016, which means that all Legionella pneumophila cases were empirically treated with...
ciprofloxacin. The CURB-65 scores for these five cases were 0, 0, 1, 2 and 3.

In conclusion, we observed that in 57% of patients who received ciprofloxacin combination therapy for CAP, the prescription was not in accordance with the 2011 guideline for hospitalised CAP patients. In this subgroup of patients who were not treated according to the guideline, testing for *Legionella* spp. was performed in 66% of the cases. With an incidence of *Legionella* less than previously assumed and a more generous use of ciprofloxacin in CAP patients than the 2011 guideline instructs, we fully agree with the 2016 SWAB/NVALT guideline update.

A more restrictive use of ciprofloxacin is warranted. Efforts to implement this new guideline and to adhere to restrictive use of quinolones in patients with CAP are urgently needed. Since *Legionella* cases, as described in our study, will be found with any CURB-65 score, we recommend to perform *Legionella* diagnostics in case of risk factors for *Legionella* pneumonia. In patients admitted to the ward, doctors should await the results of this testing without empirically start ciprofloxacin treatment.

### Table 1. Baseline characteristics of the patients who received either guideline-based or non-guideline-based treatment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treatment with ciprofloxacin was not guideline-based&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Treatment with ciprofloxacin was guideline-based&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>n = 119 (57%)</td>
<td>n = 91 (43%)</td>
</tr>
<tr>
<td>Male</td>
<td>78 (66%)</td>
<td>60 (66%)</td>
</tr>
<tr>
<td>CURB-65 score&lt;sup&gt;c&lt;/sup&gt;</td>
<td>n = 114&lt;sup&gt;1&lt;/sup&gt;</td>
<td>n = 88&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>CURB-65 score of 0</td>
<td>26 (23%)</td>
<td>0</td>
</tr>
<tr>
<td>CURB-65 score of 1</td>
<td>50 (44%)</td>
<td>0</td>
</tr>
<tr>
<td>CURB-65 score of 2</td>
<td>38 (33%)</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>CURB-65 score of 3</td>
<td>0</td>
<td>53 (60%)</td>
</tr>
<tr>
<td>CURB-65 score of 4</td>
<td>0</td>
<td>28 (32%)</td>
</tr>
<tr>
<td>CURB-65 score of 5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diagnostics for <em>Legionella</em> spp.</td>
<td>n = 119</td>
<td>n = 91</td>
</tr>
<tr>
<td>Any test for <em>Legionella</em> spp.</td>
<td>79 (66%)</td>
<td>60 (66%)</td>
</tr>
<tr>
<td>Performed Legionella urine antigen test</td>
<td>65 (55%)</td>
<td>51 (56%)</td>
</tr>
<tr>
<td>Performed PCR testing for <em>L. pneumophila</em> and <em>Legionella</em> spp.</td>
<td>42 (35%)</td>
<td>29 (32%)</td>
</tr>
<tr>
<td>Positive test for <em>L. pneumophila</em></td>
<td>3 (3%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

Data are n (%) or median (interquartile range).

<sup>a</sup>The CURB-65 score is calculated by assigning 1 point each for confusion, urea ≥ 7.0 mmol/l, respiratory rate ≥ 30/min, either a systolic blood pressure ≤ 90 mmHg or a diastolic blood pressure ≤ 60 mmHg, and age ≥ 65 years.

<sup>b</sup>Treatment with ciprofloxacin is guideline-based if: CURB-65 score is either > 2 OR CURB-65 score = 2 with the presence of a risk factor for *Legionella* infection (recent travel abroad, *Legionella* epidemic or treatment failure of beta-lactam).

<sup>c</sup>indicates five incomplete CURB-65 scores, <sup>d</sup>indicates three incomplete CURB-65 scores.

### REFERENCES