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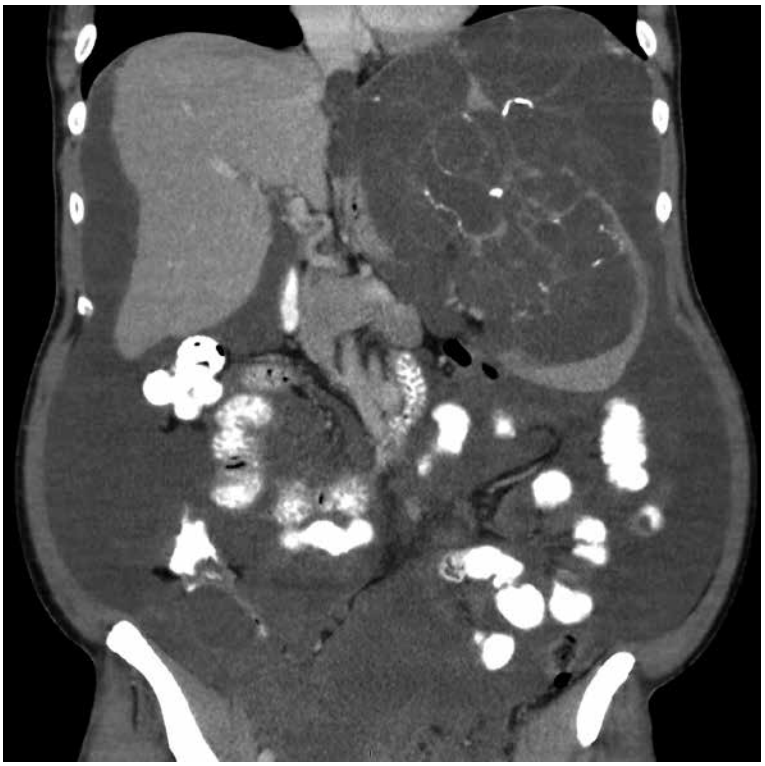

A man with an increase abdominal girth; what is your diagnosis?

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EDITORIAL

The new hepatitis C era: The guidelines are now available, reimbursement not yet...

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Berden and colleagues have taken up the challenge to guide clinicians during the use of sofosbuvir for the treatment of hepatitis C virus (HCV) as soon as its reimbursement is in place in the Netherlands.[1] Sofosbuvir is the first of more than ten new HCV direct antiviral agents (DAAs) in phase III of clinical evaluation. Many of these DAAs can be expected to get European Medicines Agency (EMA) approval within the next 24 months. It is a daunting task to keep up with the flood of new data on these DAAs. As such, a HCV treatment guideline will only be handy if it is a truly living online document that is updated as soon as another new DAA becomes EMA approved and reimbursed in the Netherlands. This is nicely illustrated by the fact that simeprevir and daclatasvir became EMA approved (but not yet reimbursed) in between the first and the second submission of this guideline to *the Netherlands Journal of Medicine*. Likewise, other tools are becoming available to assist physicians when they are confronted with a particular HCV-infected patient. The 'sustained virological response (SVR) predictor' is a useful example. It provides the best estimate of treatment success with EMA-approved drugs while taking patient characteristics (cirrhosis, genotype, interferon naive or not) into account.[2]

The benefits of these upcoming HCV treatment options are crystal clear: cure rates above 90% and very few side effects in comparison with peginterferon-based therapy. However, with the current price of € 598 per 400 mg tablet and € 50,872 for a 12-week therapy, sofosbuvir is almost 50 times(!) more expensive than gold.[3] It is not surprising that the cost-effectivity and budget impact of these DAAs will be driving a significant part of the future debate on who, when and how to treat. In high prevalence countries, such as Spain or Italy, treating all HCV-infected patients will have a huge budget impact. With this in mind, it is unfortunate that the new Dutch guideline gives very little insight into the costs of the different treatment options.

One could argue that a physician treating an individual patient should not consider costs. But what if, with the current price setting in mind, some of the suggested treatment options in the guideline can in advance be considered not cost-effective? Sofosbuvir-based HCV genotype 1 treatment is probably cost-effective for patients with significant fibrosis.[4,5] However, for HCV genotypes that are clearly more susceptible to interferon the picture is very different. Based on the new Dutch guideline, we performed a simplified cost-effectivity calculation for treatment-naive patients with genotype 3 (30% of the Dutch HCV population). Taking into account factors such as the substantial decrease in quality of life during peginterferon-ribavirin therapy, the lower cure rates in comparison with a 12-week sofosbuvir-peginterferon-ribavirin course (and therefore the need for retreatment with sofosbuvir in 30% of the patients), the costs per quality-adjusted life year (QALY) remained above 100,000 euro. The costs per QALY would increase even more if, as some physicians propose, the peginterferon-free 24-week sofosbuvir regimen is given to all. Of course, some patients are clearly interferon ineligible and should not be withhold access to interferon-free new therapies. Also, with other new DAAs to come over the next two years, supply and demand will enter the HCV market and eventually, an interferon-free treatment should become available for all patients. A true debate on the cost-effectivity of the new DAAs is urgently needed. This exercise should also clearly take into account that in certain patient populations (e.g. homosexual men or active intravenous drug users) there may well be substantial indirect cost-savings as well, through the prevention of ongoing HCV transmission.

HCV is also a very significant problem in the HIV-positive patient population in the Netherlands. Within HIV-positive patients, the majority of new HCV infections are no longer seen in (ex) intravenous drug users, but in homosexual men. In an ongoing Dutch study on acute HCV in HIV-positive men the incidence of sexually acquired

HCV is extremely high at 1.5% per year. In the ten study centres 95 (!) newly acquired HCV infections were diagnosed in the first year.[6] Breaking the chain of onward HCV transmission in this patient group may finally become possible when new DAA and peginterferon-free regimens become available and reimbursed. As such, it is unfortunate that the new guideline does not yet mention the management of HCV in HIV co-infected patients.

Berden and colleagues used the GRADE quality of evidence classification. In this form of classification a study that is a non-randomised clinical trial is per definition of low evidence (C). This may lead to very contra-intuitive gradings; in the POSITRON study, 17 patients received sofosbuvir and eight received placebo. The study was randomised and therefore received a grade B (moderate quality of evidence). When a disease, such as chronic HCV, is studied that does not cure spontaneously and 89% of the 292 patients are cured, as in the NEUTRINO clinical trial, GRADE classifies this study as grade C (low quality of evidence) just because it is a non-randomised single-arm study. It is clear that for non-randomised studies the use of the GRADE classification should be refined and is not very useful.[7]

In the light of the substantial treatment costs, well-founded answers should be given when the use of DAAs such as sofosbuvir with peginterferon (€ 53,000, SVR 92% for genotype 3), or without peginterferon (€ 102,000, SVR 94% for genotype 3) is discussed with the well-informed patient. The current article by Berden and colleagues will be helpful if the authors keep their promise and keep the guideline up-to-date.

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SPECIAL REPORT

Dutch guidance for the treatment of chronic hepatitis C virus infection in a new therapeutic era

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ABSTRACT

Background: A new era for the treatment of chronic hepatitis C is about to transpire. With the introduction of the first-generation protease inhibitors the efficacy of hepatitis C treatment improved significantly. Since then, the therapeutic agenda has moved further forward with the recent approval of sofosbuvir and the expected approval of agents such as simeprevir and daclatasvir. This paper, developed parallel to the approval of sofosbuvir, is to serve as a guidance for the therapeutic management of chronic hepatitis C.

Methods: We performed a formal search through PubMed, Web of Science and ClinicalTrials.gov to identify all clinical trials that have been conducted with EMA-approved new agents in hepatitis C; for this version (April 2014) we focused on sofosbuvir. For each disease category, the evidence was reviewed and recommendations are based on GRADE.

Results: We identified 11 clinical trials with sofosbuvir and for each disease category recommendations for treatment are made. Not all disease categories were studied extensively and therefore in some cases we were unable to provide recommendations.

Conclusion: The recent approval of sofosbuvir will most likely change the therapeutic landscape of chronic hepatitis

C. The use of sofosbuvir-containing regimens can shorten the duration of therapy, increase efficacy and result in less side effects, compared with standard of care. The efficacy relative to standard of care needs to be weighed against the increased costs of sofosbuvir. With future approval of the other direct-acting antivirals, the outcome of hepatitis C treatment will likely improve further and this guidance will be updated.

KEYWORDS

Direct-acting antivirals, guidance, hepatitis C, sofosbuvir

INTRODUCTION

The recent approval of sofosbuvir (NS5B polymerase inhibitor) and the expected approval of other direct-acting antivirals (DAAs) such as simeprevir (protease inhibitor) and daclatasvir (NS5A inhibitor) will change the therapeutic arena for chronic hepatitis C.[1] Until 2012 the treatment of chronic hepatitis C consisted of pegylated interferon with ribavirin (PR) for 24 to 48 weeks.[2] As of April 2012 two first-generation protease inhibitors, telaprevir and boceprevir, were approved for reimbursement in the Netherlands for patients infected with hepatitis C virus (HCV) genotype 1.[3] These agents improved efficacy[3] but their safety profile was poor, especially in cirrhotic patients.[4-6]

In the Netherlands, the estimated hepatitis C seroprevalence is 0.1-0.4%, and the highest prevalence is seen in first-generation migrants from HCV-endemic countries.[7-9] Approximately 50% of Dutch patients are infected with genotype 1, 30% with genotype 3, 10% with genotype 2 and 10% with genotype 4.[10]

Sofosbuvir can be regarded as a game changer;[1] it is an orally administered nucleotide polymerase inhibitor, has pangenotypic activity *in vivo*, a high barrier to resistance and an acceptable safety profile.[11] Approval of other drugs in different classes of DAAs may be expected, first of all simeprevir (during revision approved) and daclatasvir. Additional drugs belonging to the protease inhibitor class (asunaprevir, ABT -450/r), the NS5A class (ledipasvir, ombitasvir) and the non-nucleoside polymerase inhibitor class (dasabuvir) are in later stages of clinical development.[1]

This paper may serve as a current guidance for the therapeutic management of chronic hepatitis C. This update of the earlier guidance[3] is necessary given the wealth of new information that has become available since. As a static version will become outdated, we encourage to review the most current version on the websites of the Netherlands Association of Hepato-gastroenterologists (NVMDL) or the Netherlands Association of Internal Medicine (NIV).[12]

METHODS

We performed a formal search through the databases PubMed, Web of Science and ClinicalTrials.gov to identify all relevant clinical trials performed with sofosbuvir, peginterferon and/or ribavirin for this version (April 2014). In addition we searched for future therapies and for the product characteristics provided by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Opinions, letters, narrative reviews, pre-clinical studies and articles in another language than English, Dutch or German were excluded. The search string is attached in *supplementary file 1*. We limited the search for patients with HCV mono-infection. For each disease category (treatment-naive, treatment-experienced and cirrhotic patients) the evidence was reviewed by the first and second author. The treatment-experienced category consists of patients with a prior relapse, prior partial response or prior null response. Sustained virological response (SVR) is defined as an HCV RNA below the lower limit of quantification at 12 weeks after the end of treatment. We listed the results of all individual trials in tables according to disease category. The level of evidence was formulated based on the GRADE method with the quality of evidence and a strength of recommendation (*supplementary file 2*).[13] The recommendations in this paper went through a formal approval process and were vetted by individual experts and all members of the NVMDL and representatives of the NIV.

RESULTS

We formulated recommendations on the basis of the available evidence and information from the label of sofosbuvir. The recommendations are given for each disease category. When no recommendation is given, treatment can be deferred or we refer to the earlier guideline.[3] First, all currently approved agents and expected agents are listed, followed by recommended treatment options for the different HCV genotypes once sofosbuvir is approved. Recommendations are valid for all patients with an indication for treatment as stipulated by the earlier guideline.[3]

List of currently approved drugs for treatment of chronic HCV infection:

- Peginterferon: polyethylene glycol attached to interferon-α
  - Peginterferon α -2a: 180 μg/week

  - Peginterferon α -2b: 1.5 μg/kg/week
- Ribavirin: nucleoside analogue, weight-based dose (< 75 kg 1000 mg/day and ≥ 75 kg 1200 mg/day, divided over two doses)
- Protease inhibitors (-previr):
  - Simeprevir (during revision approved, will be included in updated version)
  - Telaprevir: 2250 mg/day, divided over two or three doses
  - Boceprevir: 2400 mg/day, divided over three doses
- Nucleotide polymerase inhibitor (-buvir):
  - Sofosbuvir: 400 mg/day, in one dose
    No data in patients with renal impairment are available (eGFR < 30 ml/min/m^2)

List of HCV drugs in development:
This list is not exhaustive and can be expanded; we aimed to include drugs that are in phase III development.[1]

- Protease inhibitors (-previr):
  - Asunaprevir
  - Faldaprevir
  - ABT-450/r (ritonavir-boosted)
  - MK-5172
- NS5A inhibitors (-asvir):
  - Daclatasvir
  - Ledipasvir
  - Ombitasvir (ABT-267)
  - MK-8742
- Non-nucleoside polymerase inhibitors (-buvir):
  - Dasabuvir (ABT-333)

Watchful waiting
Watchful waiting is a preferred strategy in patients who do not have an urgent indication for treatment based on the earlier guideline,[3] in patients where no recommendation is given or when the quality of evidence is low and the strength of recommendation is weak (Level: C2). There are several arguments in favour of this strategy: (A) not all patient groups are represented in clinical trials, therefore the evidence for recommendations is weak in certain disease categories, (B) with the introduction of sofosbuvir we still need pegylated interferon and ribavirin in many patients and (C) improved efficacy and reduced toxicity is expected from interferon-free combinations of DAAs likely to be approved in the near future.[1]

Recommendations by HCV genotype, disease stage and treatment history

Genotype 1 treatment-naive patients

Recommendation: Sofosbuvir, peginterferon and weight-based ribavirin for 12 weeks (Level: B1)

Several trials have been performed in genotype 1 treatment-naive patients (*figure 1*). The recommended therapy was studied in two trials: NEUTRINO and ATOMIC. The NEUTRINO trial was a single-group open-label trial that achieved 89% SVR.[14] Patients without cirrhosis obtained 90% SVR in the ATOMIC trial. There was no additional benefit (i.e. no difference in SVR) for extension of treatment to 24 weeks or by extension with sofosbuvir monotherapy or sofosbuvir and ribavirin (n = 264).[15] The dose of sofosbuvir was determined on the basis of the PROTON study where 200 and 400 mg of sofosbuvir were compared. Here, the SVR rate was irrespective of the dose of sofosbuvir; however, three patients in the 200 mg group had a viral breakthrough, hence the selection of 400 mg.[16] Only one trial was of high quality,[16] the other trials were open-label trials of a low to moderate quality.[13]

Genotype 1 treatment-experienced patients

Recommendation: No recommendation based on data

The ELECTRON trial was the only trial that included treatment-experienced genotype 1 patients; these patients received sofosbuvir with ribavirin (12 weeks), only one of ten patients achieved SVR.[17] The label recommends consideration of treatment with sofosbuvir, peginterferon and ribavirin for 12 weeks or extension to 24 weeks,[18] but in our opinion more data are needed.

Genotype 1 cirrhotic patients

Recommendation: Watchful waiting (Level: C1)

Two clinical trials included patients with cirrhosis; the NEUTRINO trial reached 80% SVR with sofosbuvir on top of PR[14] and three of six cirrhotic patients with unfavourable characteristics achieved SVR with sofosbuvir and ribavirin in a single-centre trial.[19] The quality of evidence for sofosbuvir is low, the toxicity of the previous standard of care in cirrhotic patients is high[4] and future agents (e.g. simeprevir) are promising, hence watchful waiting is recommended.

Future perspective

For genotype 1 patients, multiple trials are currently underway; promising agents are simeprevir, asunaprevir, ABT-450/r (protease inhibitors), daclatasvir, ledipasvir, ombitasvir (NS5A inhibitors) and dasabuvir (non-nucleoside polymerase inhibitor). All oral treatment is expected to become possible in the near future for both treatment-naive and treatment-experienced patients.

Simeprevir and sofosbuvir with or without ribavirin were studied in the COSMOS trial in two cohorts, in prior null responders with F0-2 fibrosis (cohort 1) and in treatment naive or prior null responders with F3-4 fibrosis (cohort 2). High SVR rates were seen in cohort 1 (91-100%)[20] and cohort 2 (94-96%).[21,22] Therefore the combined treatment of simeprevir and sofosbuvir can be a reasonable option for these categories of patients in the near future. Simeprevir with PR has been studied in the ASPIRE, PILLAR and PROMISE studies and high SVR rates of 70-85% are seen

Figure 1. *Trials in HCV genotype 1 patients*

Trial	Regime (weeks) 0 4 8 12 24 // 48	n	SVR	SVR (95% CI) 0 50 100	QoE
Genotype 1, treatment naive					
PROTON	SOF(200)+PR / PR / PR	48	90%		A
	SOF(400)+PR / PR / PR	47	91%		A
	placebo + PR / PR	26	58%		A
NEUTRINO	SOF+PR	292	89%		C
ELECTRON	SOF(+RBV)	25	84%		C
ATOMIC	SOF+PR	52	90%		B
	SOF+PR	109	93%		B
	SOF+PR / SOF(+RBV)	155	91%		B
Osinusi et al.[ʃ]	SOF+RBV(wb)	10	90%		C
	SOF+RBV(wb)	25	68%		C
	SOF+RBV(600)	25	48%		C
Genotype 1, treatment experienced					
ELECTRON	SOF+RBV	10	10%		C
Genotype 1, cirrhosis					
NEUTRINO	SOF+PR	54 †	80%		C
Osinusi et al.*[ʃ]	SOF+RBV(wb)	6 †	50%		C
	SOF+RBV(600)	7 †	29%		C

PR = pegylated interferon with ribavirin; QoE = Quality of Evidence (A: high, B: moderate, C: low); RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virological response; wb: weight-based; *calculated 95% CI, [ʃ]first cohort early-moderate fibrosis; second and third cohort unfavourable characteristics. In cirrhotics: †treatment naive.

in cirrhotic patients with prior relapse or prior partial response.[23-25] Clinical trials with simeprevir have shown that a Q80K mutation in genotype 1a patients significantly reduces the efficacy of the treatment.[26]

Sofosbuvir plus daclatasvir with or without ribavirin for 12 or 24 weeks was studied in the AI444040 study, 126 treatment-naive genotype 1 patients achieved 98% SVR. Furthermore 41 patients who failed therapy with telaprevir or boceprevir had 98% SVR with 24 weeks of sofosbuvir and daclatasvir with or without ribavirin. Cirrhotic patients were excluded.[27] Currently a compassionate use program of sofosbuvir and daclatasvir with or without ribavirin for Child-Pugh C patients is available.

The combination of an NS5B polymerase inhibitor and an NS5A inhibitor is also being studied in the LONESTAR, ION-1, ION-2 and ION-3 studies. The LONESTAR is a single-centre open-label study in genotype 1 treatment-naive patients and patients with virological failure on protease inhibitors. An SVR of 95-100% (n = 100) with different regimens (i.e. sofosbuvir/ledipasvir with or without ribavirin, 8 or 12 weeks) was reached.[28] In the ION-1 and ION-2 trials, SVR was reached in 94-98% of the patients with 12 weeks of sofosbuvir/ledipasvir with or without ribavirin.[29,30] In the ION-3 trial treatment-naive non-cirrhotic patients achieved 94% SVR with 8 weeks of sofosbuvir/ledipasvir.[31] Phase 2a trials have been performed with daclatasvir and asunaprevir in combination with PR or the non-nucleoside polymerase inhibitor BMS-791325 in prior null responders and treatment-naive patients for 12-24 weeks. High SVR rates, 92-100%, were achieved.[32-34] Three

studies (n = 571, n = 297 and n = 473) evaluated multiple regimens with ABT-450/r, dasabuvir and ombitasvir with or without ribavirin in different combinations and durations. High SVR rates (83-97%) were seen in treatment-naive and treatment-experienced non-cirrhotic patients.[35-37] The TURQUOISE-II trial studied the same regimen (with ribavirin) in compensated cirrhotic patients for 12 (n = 208) and 24 (n = 172) weeks. SVR was achieved in 92% and 96% of the patients, respectively.[38]

Genotype 2 treatment-naive patients

Recommendation: Sofosbuvir and weight-based ribavirin for 12 weeks (Level: A1)

Patients with an HCV genotype 2 infection have an SVR rate of 74-83% with PR for 24 weeks.[3,39,40] Multiple trials with sofosbuvir have been performed in treatment-naive genotype 2 patients (*figure 2*). Two trials of high quality and one of low quality studied the recommended interferon-free regimen (POSITRON, FISSION and VALENCE) with consistent good results. The POSITRON trial included patients for whom interferon was not an option and reached 93% SVR irrespective of cirrhosis.[11] In the FISSION trial SVR was reached in 97% of patients, while in patients treated with peginterferon and ribavirin (800 mg) for 24 weeks SVR was achieved in 78%.[14] The results of the VALENCE trial are similar to FISSION and POSITRON for the recommended regimen.[41,42] Addition of peginterferon showed no improved SVR rates.[16,17] In conclusion, sofosbuvir with ribavirin for 12 weeks in genotype 2 patients was effective in high-quality trials with implications for clinical practice because of an interferon-free regimen with a shorter treatment duration than the previous standard of care.[3]

Genotype 2 treatment-experienced patients

Recommendation: Sofosbuvir and weight-based ribavirin for 12 weeks (Level: B1)

In the FUSION trial, genotype 2 patients were treated with either 12 or 16 weeks of sofosbuvir and ribavirin. Patients in the 12-week arm received four weeks of placebo, they reached 86% SVR and in the 16-week arm this was 94%. For non-cirrhotic patients the FUSION trial failed to demonstrate additional value of extending the treatment to 16 weeks, hence the recommendation of 12 weeks.[11] The POSITRON included 17 patients with unacceptable side effects in prior treatment and they achieved an SVR of 78% with sofosbuvir and ribavirin.[11] The results of the VALENCE trial demonstrated a 90% SVR with the recommended regimen.[18,42] In another trial there was no additional value of peginterferon.[43] Again this treatment has significant implications for clinical practice because of the high SVR rates without interferon and shorter treatment duration. The trials were of high[11] and low quality[41,43] with consistent results.

Genotype 2 cirrhotic patients

Recommendation: Sofosbuvir and weight-based ribavirin for 12 weeks (Level: B1)

There are four trials that evaluated sofosbuvir and ribavirin for 12 weeks in cirrhotic genotype 2 patients, mainly treatment-naive patients were studied. The FISSION demonstrated an SVR of 83% (n = 12), treatment with peginterferon and ribavirin (800 mg) for 24 weeks led to 62% SVR (n = 13).[14,18] The POSITRON trial showed an SVR of 94%. In treatment-experienced patients with cirrhosis an extension of duration of treatment from 12 to 16 weeks led to an improvement in SVR from 60% (n = 10) to 78% (n = 9) in the FUSION trial.[11] The VALENCE trial shows 82% SVR in 11 cirrhotic patients with sofosbuvir and ribavirin (12 weeks).[18,44] All trials included only a small number of patients, but implications for clinical practice are high as treatment is warranted and toxicity is expected to be less than with standard of care.

Future perspective

For genotype 2 patients the regimen of sofosbuvir with ribavirin leads to high SVR rates. Also, the AI444040 trial studied 26 treatment-naive genotype 2 patients; 24 (92%) achieved SVR with different regimens consisting of sofosbuvir and daclatasvir with or without ribavirin for 24 weeks. Cirrhotic patients were excluded.[27]

Genotype 3 treatment-naive patients

Recommendation:

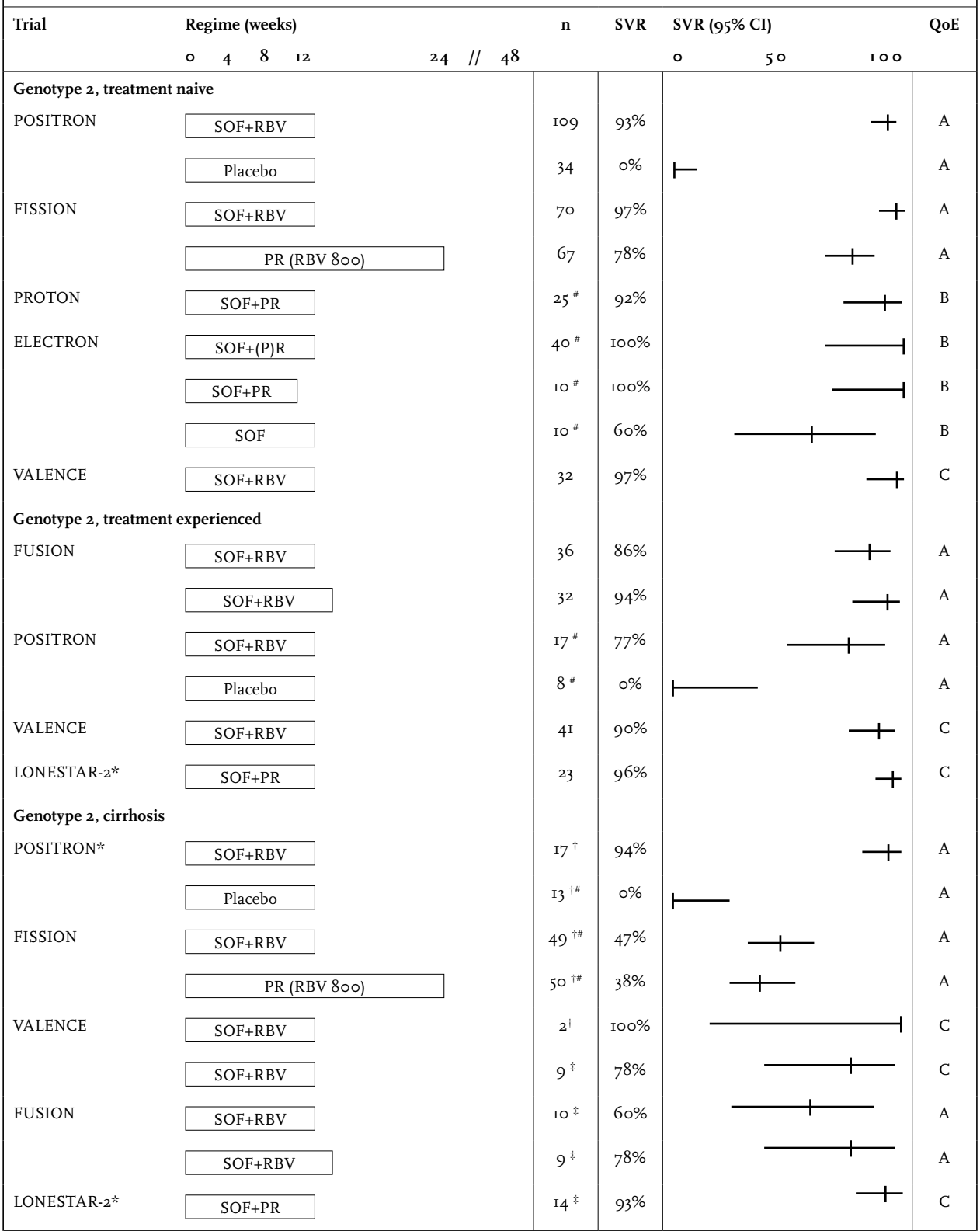
- *Watchful waiting*
- *Peginterferon and ribavirin (800 mg) for 24 weeks*
- *Sofosbuvir and weight-based ribavirin for 24 weeks*
- *Sofosbuvir, peginterferon and weight-based ribavirin for 12 weeks*

(Level A2)

For genotype 3 patients, several options for treatment are available and the physician has to decide which strategy is currently better for the individual patient. Historically genotype 2 and genotype 3 patients achieve an SVR of 70-80% with peginterferon and ribavirin (800 mg) for 24 weeks.[3]

Different trials have been performed in genotype 3 patients; all trials with 12 weeks of sofosbuvir and ribavirin fail to show superiority in comparison with PR treatment (*figure 3*).[14] The addition of peginterferon or extension of treatment to 24 weeks showed improved results. In the ELECTRON trial, 25 patients received 12 weeks of sofosbuvir and ribavirin combined with peginterferon for 0, 4, 8 or 12 weeks: all patients achieved SVR.[17] The VALENCE trial obtained 94% SVR in 105 patients with sofosbuvir with ribavirin for 24 weeks.[18,42] Because of the above-mentioned results peginterferon with ribavirin (800 mg) for 24 weeks remains an option for therapy, ribavirin should be weight based in patients

Figure 2. *Trials in HCV genotype 2 patients*



PR = pegylated interferon with ribavirin; QoE = Quality of Evidence (A: high, B: moderate, C: low); RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virological response; *calculated 95% CI, # data of genotype 2 and 3 combined. In cirrhotics: † treatment naive, ‡ treatment experienced.

with baseline characteristics associated with a poor response.[3] Other options are watchful waiting, sofosbuvir with ribavirin for 24 weeks or sofosbuvir with PR for 12 weeks. The choice for one of the regimens is dependent on the individual patient, bearing in mind the higher costs of sofosbuvir.

Genotype 3 treatment-experienced patients

Recommendation: Watchful waiting

Alternative strategy: Sofosbuvir and weight-based ribavirin for 24 weeks OR sofosbuvir, peginterferon and weight-based ribavirin for 12 weeks (Level: B2)

Results of sofosbuvir for treatment-experienced genotype 3 patients are disappointing with high imprecision; only the VALENCE and LONESTAR-2 trials show acceptable results but are of low quality. The FUSION trial showed that extension of treatment by 4 weeks led to improvement of SVR.[11] Extension to 24 weeks was done in the VALENCE study and an SVR of 79% was achieved, while for the non-cirrhotic patients the SVR rate was 87%.[18,42] The LONESTAR-2 trial showed an SVR of 83% in 24 patients treated with sofosbuvir and PR for 12 weeks.[43] In the near future more effective combinations of DAAs are expected. Therefore, the general recommendation is watchful waiting. As an alternative strategy sofosbuvir with ribavirin for 24 weeks or sofosbuvir with PR for 12 weeks may be considered.

Genotype 3 cirrhotic patients

Recommendation: Watchful waiting

Alternative strategy: Sofosbuvir and weight-based ribavirin for 16 weeks OR sofosbuvir and weight-based ribavirin for 24 weeks (Level: B2)

Genotype 3 cirrhotic patients were treated with sofosbuvir in five trials with moderate SVR rates.

The FUSION trial showed an SVR of 19% with 12 weeks of sofosbuvir and ribavirin in treatment-experienced cirrhotic patients; extension of treatment to 16 weeks showed an SVR of 61%. The VALENCE trial studied 24 weeks of sofosbuvir and ribavirin in 60 cirrhotic patients, with 92% SVR in treatment-naive patients and 62% in treatment-experienced patients.[18]

Based on the above results with small numbers of patients, we advise watchful waiting as the recommended strategy since SVR rates are rather low, mainly in treatment-experienced patients and sofosbuvir is expensive. Alternative regimens are sofosbuvir and ribavirin for 16 weeks or 24 weeks.

Future perspective

Daclatasvir is one of the agents that are expected to be approved in the near future. The COMMAND GT 2/3 study included 151 genotype 2 and 3 patients and these patients received either 12 or 16 weeks of daclatasvir with PR or 24 weeks placebo with PR. SVR rates were 69% (12 weeks), 67% (16 weeks) and 59% (placebo). Treatment failure was mainly due to relapse in cirrhotic patients in the 12-week group.[45] The combination of sofosbuvir and daclatasvir with or without ribavirin for 24 weeks does hold promise for treatment-naive genotype 3 patients as SVR rates of 89% can be reached.[27] Treatment-naive genotype 3 patients received sofosbuvir/ledipasvir with or without ribavirin in the ELECTRON-2 trial (12 weeks). Dual therapy reached 64% SVR (n=25) while triple therapy reached 100% SVR (n=26).[46]

Genotype 4 treatment-naive patients

Recommendation: Sofosbuvir, peginterferon and weight-based ribavirin for 12 weeks. (Level: C1)

The recommended regimen is being studied in the NEUTRINO trial, 28 patients were treated with sofosbuvir and PR for 12 weeks and reached 96% SVR.[14] Extension of therapy to 24 weeks did not show an improved effect.[15] Egyptian patients (n = 28) received an interferon-free regimen for 12 or 24 weeks and achieved 79% and 100% SVR, respectively.[47] In general, data are scarce (*figure 4*) but in view of the high SVR rates sofosbuvir-based treatment is recommended.

Genotype 4 treatment-experienced patients

Recommendation: No recommendation based on data

There are no published data on sofosbuvir-based treatment available for treatment-experienced genotype 4 patients. The most recent data of the Egyptian study showed 59% SVR (n = 17) with 12 weeks of sofosbuvir and ribavirin and 87% SVR (n = 15) with 24 weeks of sofosbuvir and ribavirin.[47,48] The label recommends sofosbuvir and PR for 12 weeks, but more data are needed.

Genotype 4 cirrhotic patients

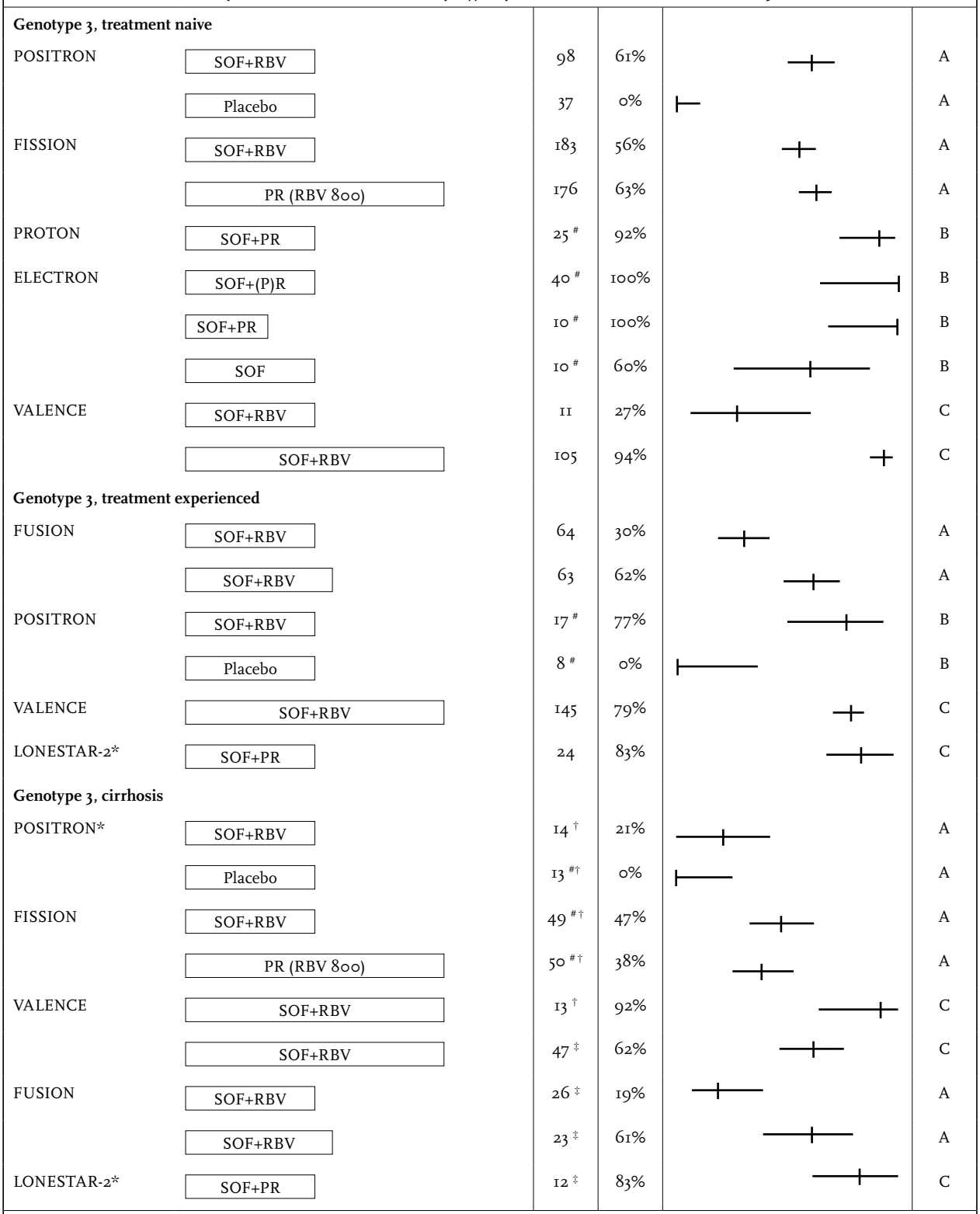
Recommendation: No recommendation based on data

Only a limited number of cirrhotic genotype 4 patients have been studied. The NEUTRINO trial included two cirrhotic genotype 4 patients of whom one achieved SVR with sofosbuvir and PR for 12 weeks.[14] In the Egyptian study treatment-naive cirrhotic patients achieved 33% (n = 3) and 100% (n = 3) SVR with 12 and 24 weeks of sofosbuvir and ribavirin. The SVR rates in treatment-experienced patients were 50% and 100% in both groups (n = 8).[47]

Future perspective

Simeprevir with PR (24 or 48 weeks) is studied in genotype 4 patients, overall 65% of the patients reached SVR with higher SVR rates in treatment-naive and relapse patients (83% and 86%).[49] Asunaprevir with PR has been studied in 18 genotype 4 patients for 24 weeks and 89% reached SVR, the control group consisted of seven patients of whom

Figure 3. *Trials in HCV genotype 3 patients*



PR = pegylated interferon with ribavirin; QoE = Quality of Evidence (A: high, B: moderate, C: low); RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virological response; *calculated 95% CI, # data of genotype 2 and 3 combined. In cirrhotics: † treatment naive, ‡ treatment experienced.

43% reached SVR with PR for 48 weeks.[50] Furthermore daclatasvir was studied in 24 treatment-naive genotype 4 patients, 67% achieved SVR with 20 mg daclatasvir and 100% achieved SVR with 60 mg daclatasvir with PR for 24 weeks.[51] Daclatasvir with asunaprevir and BMS-791325 were studied in 12 patients, 11 achieved SVR and 1 patient is still in follow-up.[52] The PEARL-I study included 86 treatment-naive genotype 4 patients who received ABT-450/r plus ombitasvir with or without ribavirin (12 weeks), 91-100% SVR was achieved.[53] Patient numbers are limited but in view of the high SVR rates of future therapy, watchful waiting can be considered in genotype 4 patients until further data allow approval of newer DAAs.

Genotype 5, 6

Data from well-powered clinical comparative trials for genotype 5 and 6 patients are lacking. We think it is unlikely that such data will become available in the near future for the novel DAAs. Therefore we consider it acceptable to use treatment results for genotype 1 as a template for treatment of genotype 5 and 6.

Genotype 5, 6 treatment-naive patients

Recommendation:

- *Genotype 5: No recommendation based on data, consider genotype 1 treatment regimen as template (Level: C2)*

Figure 4. *Trials in HCV genotype 4, 5 and 6 patients*

Trial	Regime (weeks) 0 4 8 12 24 // 48	n	SVR	SVR (95% CI) 0 50 100	QoE
Genotype 4, treatment naive					
NEUTRINO*	SOF+PR	28	96%		C
ATOMIC	SOF+PR	11	82%		C
Ruane et al.*	SOF+RBV	14	79%		C
	SOF+RBV	14	100%		C
Genotype 4, treatment experienced					
Ruane et al.*	SOF+RBV	17	59%		C
	SOF+RBV	15	87%		C
Genotype 4, cirrhosis					
NEUTRINO*	SOF+PR	2 †	50%		C
Ruane et al. *	SOF+RBV	3 †	33%		C
	SOF+RBV	4 ‡	50%		C
	SOF+RBV	3 †	100%		C
	SOF+RBV	4 ‡	100%		C
Genotype 5 and 6, treatment naive					
NEUTRINO*	SOF+PR	7	100%		C
ATOMIC	SOF+PR	5	100%		C
Genotype 5 and 6, treatment experienced					
No available trials					

PR = pegylated interferon with ribavirin; QoE = Quality of Evidence (A: high, B: moderate, C: low); RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virological response; *calculated 95% CI, if 100% SVR then no CI could be calculated. In cirrhotics: † treatment naive, ‡ treatment experienced.

- *Genotype 6: sofosbuvir, peginterferon and weight-based ribavirin for 12 weeks (Level: C2)*

Only 12 treatment-naive patients with genotype 5 or 6 have been treated in two trials (NEUTRINO and ATOMIC). In the NEUTRINO trial six genotype 6 patients and one genotype 5 patient were treated with 12 weeks of sofosbuvir and PR and all patients achieved SVR.[14] In the ATOMIC trial only five patients with genotype 6 received sofosbuvir with PR for 24 weeks, all achieved SVR.[15] More data are needed, however, considering the high SVR rates a sofosbuvir-based treatment is recommended for genotype 6.

Genotype 5,6 treatment-experienced patients

Recommendation: No recommendation based on data, consider genotype 1 treatment regimen as template (Level: C2)

There are no data on sofosbuvir-based treatment available for treatment-experienced genotype 5 or 6 patients.

Genotype 5, 6 cirrhotic patients

Recommendation: No recommendation based on data, consider genotype 1 treatment regimen as template (Level: C2)

The NEUTRINO trial included 20% cirrhotic patients but it is unknown if cirrhotic genotype 5 or 6 patients were included.[14]

Drug-drug interactions

Many of the DAAs are substrates of CYP450 and the membrane transporter P-gp; they may both be the victim of drug interactions or cause these interactions with other agents.[54,55] Sofosbuvir has a relatively mild drug interaction profile as it is only a substrate of P-gp and does not interfere with CYP450 enzymes. It is necessary to check for interacting co-medications, including over the counter drugs (e.g. St. John's Wort), before starting DAA-based HCV treatment (http://www.hep-druginteractions.org).

Summary box of recommendations for HCV monoinfected patients

Genotype	Patient group	Recommendation	Future perspective
1	Treatment naive	Sofosbuvir, peginterferon and ribavirin for 12 weeks	Daclatasvir, simeprevir, ledipasvir, asunaprevir, ABT-450/r, dasabuvir, ombitasvir
	Treatment experienced	No recommendation based on data	
	Cirrhotic	Watchful waiting	
2	Treatment naive	Sofosbuvir and ribavirin for 12 weeks	Daclatasvir
	Treatment experienced	Sofosbuvir and ribavirin for 12 weeks	
	Cirrhotic	Sofosbuvir and ribavirin for 12 weeks	
3	Treatment naive	Physician opinion to determine the strategy, options: • Watchful waiting • Peginterferon and ribavirin (800 mg) for 24 weeks • Sofosbuvir and ribavirin for 24 weeks • Sofosbuvir, peginterferon and ribavirin for 12 weeks	Daclatasvir, ledipasvir
	Treatment experienced	Watchful waiting Alternative strategy: • Sofosbuvir and ribavirin for 24 weeks OR • Sofosbuvir, peginterferon and ribavirin for 12 weeks	
	Cirrhotic	Watchful waiting Alternative strategy: • Sofosbuvir and ribavirin for 16 weeks OR • Sofosbuvir and ribavirin for 24 weeks	
4	Treatment naïve	Sofosbuvir, peginterferon and ribavirin for 12 weeks	Simeprevir, daclatasvir, asunaprevir, ABT-450/r, ombitasvir
	Treatment experienced	No recommendation based on data	
	Cirrhotic	No recommendation based on data	
5, 6	Treatment naive	Genotype 5: No recommendation based on data, consider genotype 1 treatment regimen as template Genotype 6: Sofosbuvir, peginterferon and ribavirin for 12 weeks	
	Treatment experienced	No recommendation based on data, consider genotype 1 treatment regimen as template	
	Cirrhotic	No recommendation based on data, consider genotype 1 treatment regimen as template	

DISCUSSION

The current guidance comes at a time when the landscape of HCV treatment is undergoing a rapid change. There are currently four comparable guidances, one was issued by the American Association for the Study of Liver Diseases (AASLD), one by European Association for the Study of the Liver (EASL) and the other two are guidances from Germany.[56-59] Our guidance differs from the AASLD and EASL guidances and we do not offer advice on the use of simeprevir and daclatasvir in this version. The main difference with the other guidances is that we offer the clinician the option to defer treatment in genotype 3 and some subgroups of patients. The reason is that, except for the VALENCE trial, the currently published evidence has not proved efficacy beyond standard of care. The proportion of cirrhotic patients in the various trials is disappointingly low and recommendations cannot be given for this category, with the exception of genotype 2. This contrasts with clinical practice where cirrhotic patients have the most urgent treatment indication.[3] For genotypes 5 and 6 the current evidence is poor. The AASLD, EASL and German guidances recommend sofosbuvir triple therapy for genotype 5 and 6. The consensus in the Hepatology Committee was that the evidence for sofosbuvir was acceptable for genotype 6 naive patients, while we recommend standard of care or considering the genotype 1 regimen as template for other disease categories in genotype 5 and 6. At odds with other guidances we do not recommend sofosbuvir-based treatment for genotype 1 and 4 treatment-experienced patients given the lack of evidence. This guidance only includes recommendations for HCV monoinfected patients. Sofosbuvir and other DAAs are also being studied in HIV/HCV patients; this will be updated in a new version of this guidance.

The rapid pace of development of drugs to treat HCV infection introduces not only great expectations but also uncertainty about the optimal timing to initiate therapy.[60] The key question here is which patients can benefit from the DAAs that are now available. Sofosbuvir is a first-generation polymerase inhibitor that is in the vanguard of a wave of drugs that have the potential to cure HCV. With the approval of the EMA, sofosbuvir will be released on the Dutch market soon. As medication is an important costdriver, the added efficacy of sofosbuvir relative to standard of care should be weighed carefully.[61] As the pipeline with new antiviral drugs is full and new releases can be expected in 2014 and 2015, this paper serves as a dynamic document and will be continually edited and updated.[12]

DISCLOSURES

Conflicts of interest

F.A.C. Berden: none

W. Kievit: none

L.C. Baak: was a member of the advisory board and/or received speakers fees from Gilead, Janssen, AbbVie and Bristol-Myers Squibb

C.M. Bakker: none

U.H.W. Beuers: consulting on behalf of Academic Medical Centre: Intercept, Novartis; speaking and teaching: Falk Foundation, Gilead, Intercept, Roche, Zambon

C.A. Boucher: received a research grant from MSD, is a consultant on behalf of Erasmus MC for MSD and AbbVie, received a travel grant from Gilead and is scientific director of Virology Education

J.T. Brouwer: was a member of the advisory board of MSD, Gilead, AbbVie, Janssen and Bristol-Myers Squibb; received a travel grant from MSD and Gilead

D.M. Burger: received research grants from Janssen, Merck and Roche; was a member of the advisory board of Janssen and Merck and received speakers fees from Janssen, Merck, AbbVie and Gilead

K.J.L. van Erpecum: served in the advisory boards of AbbVie and Bristol-Myers Squibb and received previous funding for research from BMS and MSD

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G.H. Koek: none

K.M.J. van Nieuwkerk: was a member of the advisory boards of Gilead, Abbvie, MSD, Janssen

H. van Soest: was a member of the advisory board of Bristol-Myers Squibb, AbbVie, Janssen and MSD

A.C.I.T.L. Tan: none

J.M. Vrolijk: none

J.P.H. Drenth: served on the advisory boards of AbbVie, BMS and Gilead; served as a consultant for Gilead; his department receives research funding from Dr. Falk, AbbVie, Ipsen, Novartis and Zambon.

Supplementary file 1. *Search*

An initial search was conducted on 25-Feb-2014 with the term: '2-((5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-ylmethoxy)phenoxyphosphorylamino) propionic acid isopropyl ester [Supplementary Concept]' as a MeSH term. Furthermore we included 'sofosbuvir OR GS-7977 OR PSI 7977 OR PSI7977 OR PSI-7977 OR Sovaldi' in our search. In total 98 articles were found in PubMed. All were scanned on title and abstract for inclusion. New results of the search were added until 8-Apr-14. For the future perspectives we searched the agents in phase III of clinical trials, including simeprevir (as MeSH combined with 'simeprevir OR TMC 435350 OR TMC435350 OR TMC-435350 OR Olysio OR TMC 435 OR TMC435 OR TMC-435', with the limit of clinical trials). We did the same for daclatasvir, ledipasvir, asunaprevir and the ABT formulations in PubMed. Clinicaltrials.gov was used to get more information about the unpublished trials. Prior to submission, the abstracts of the International Liver Congress 2014 (49th annual meeting of the European Association for the Study of the Liver) were scanned and relevant studies were included in the future perspectives of the different genotypes.

Supplementary file 2. *Evidence grading (adapted from the GRADE system)*

Level	Evidence quality	Strength of recommendation
A1	High	Strong
B1	Moderate	Strong
C1	Low	Strong
A2	High	Weak
B2	Moderate	Weak
C2	Low	Weak

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SPECIAL REPORT

To treat or not to treat

Developments in the field of advanced differentiated thyroid cancer

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ABSTRACT

Background: Thyroid cancer is the most prevalent endocrine malignancy. Based on the increased understanding of thyroid tumourigenesis, novel therapeutic agents have been identified. However, given the low incidence, the good prognosis of the majority of these tumours and the limited evidence of different treatment modalities, a wide variety of treatment strategies are available. These are mostly based on small studies, data from retrospective analyses and the particular experiences of treating physicians. We discuss the recent developments in the treatment of advanced differentiated thyroid cancer.
Case description: Three cases demonstrate the considerations involved in treatment decisions for patients with advanced thyroid cancer. The first patient achieved stable disease for over five years with different targeted therapies. The second patient shows the potential (severe) toxicity of these drugs and the third patient illustrates the indolent nature of this disease.
Conclusion: The treatment of patients with extensively metastasised thyroid cancer is very complicated. The timing of initiation of therapy and the potential toxicity of targeted therapies are important in the clinical decision to treat or not to treat because of the slowly progressive course of differentiated thyroid cancer. When targeted therapy is considered, it remains of great importance to enrol patients in clinical studies in order to further determine the position of these therapies, to develop more effective (combination) treatment schemes, and above all, to identify those patients that truly benefit.

KEYWORDS

Advanced differentiated thyroid cancer, outcome, targeted therapies, toxicity

INTRODUCTION

Thyroid cancer accounted for 95% of cancers of the endocrine system and 66% of endocrine cancer mortality in 2010.[1] The incidence of thyroid cancer is globally increasing, which is largely due to an increase in the number of detected small tumours (T1). In 2011, 185 men and 426 women were diagnosed in the Netherlands with thyroid malignancy.[2] Thyroid cancer is a heterogeneous disease that is classified into differentiated thyroid carcinoma (DTC 80-90%), undifferentiated (anaplastic) thyroid carcinoma (ATC 5-10%) and medullary thyroid carcinoma (MTC 5%). DTC covers papillary (60-70%) and follicular (also including the oncocytic variant, known as Hürthle cell carcinoma) subtypes (20-30%). The majority of DTC is slowly progressive and, when identified at an early stage, frequently cured with adequate surgical management and radioactive iodine (RAI) ablation therapy. However, metastatic DTC that has become inoperable or refractory to RAI therapy is associated with a less favourable prognosis (*table 1*). Based on the understanding of thyroid tumourigenesis, potential targets and novel therapeutic agents have been identified (*figure 1*). Based on the patients presented here, we discuss the recent developments in the treatment of advanced differentiated, RAI refractory thyroid cancer and the considerations involved in treatment decision-making.

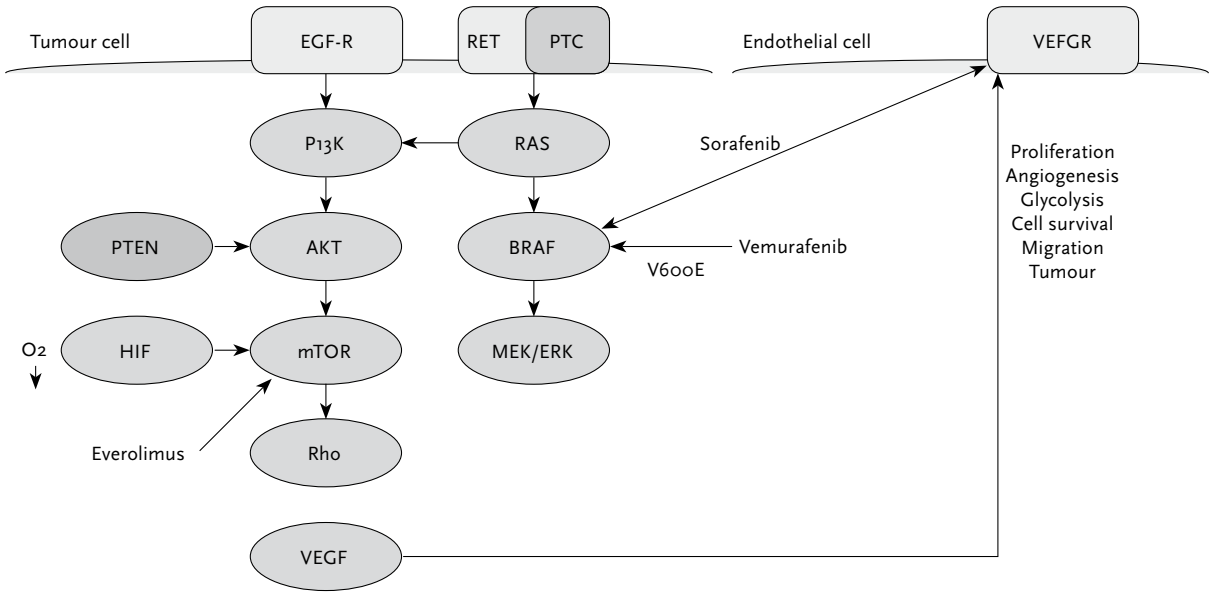
Patient A was a 47-year-old man when he was diagnosed with a multifocal papillary T2N0M0 thyroid carcinoma in 1995. He underwent a total thyroidectomy, followed by RAI ablation therapy (50 millicurie (mCi)) and thyroid-stimulating hormone (TSH) suppression therapy. Besides hypertension, his medical history revealed no other diseases. In 2002, he developed multiple lung and mediastinal lymph node metastases and was treated with additional RAI therapy (cumulative dose 545 mCi). The

Table 1. *Thyroid cancer: tumour type, age, prevalence and survival*

Tumour type		Age (years)	Prevalence	10-year survival	
				Non metastatic disease	Metastatic disease
Differentiated	Papillary Follicular	10-60 25-70	60-70% 20-30%	90-95%	5-10%
Medullary		10-60	5%	75%	10%
Anaplastic		>60	5-10%	<5%	0

Schlumberger M, Pacini F. Thyroid tumors. Paris, France: Editions Nucléon 2006.

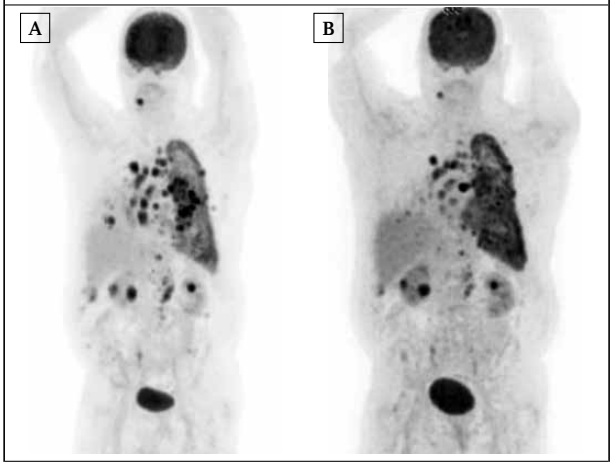
Figure 1. *Signalling pathways involved in thyroid tumourigenesis*



last post-therapeutic whole body scan was negative. In 2008 the lung metastases were progressive so he started sorafenib 400 mg twice daily in a phase II study in 2008. Revision of the tumour showed a B-type Raf kinase (BRAF) V600E mutation. Due to grade 3 diarrhoea sorafenib was reduced from 800 mg to 200 mg daily, which resulted in a partial response according to the Response Evaluation Criteria In Solid Tumours (RECIST).[3] Two years later the patient showed progressive disease with pleuritis carcinomatosis. Sorafenib was discontinued and the patient underwent pleurodesis and therapeutic punctures. After progression of his pulmonary metastases he was enrolled in a phase II trial with everolimus at the end of 2010 resulting in stable disease. He tolerated everolimus treatment well after a 50% dose reduction to 5 mg daily because of mucositis. In August 2012 the disease became progressive again and everolimus was discontinued. One month later the patient started on vemurafenib in a phase II study. He tolerated the standard dose (960 mg twice daily) well and stable disease was achieved (*figure 2*). One year after initiation of vemurafenib, he developed progressive dyspnoea and haemoptysis and died at the age of 65, most likely due to a massive haemorrhage from a pulmonary metastasis.

Patient B is a 74-year-old man diagnosed with a follicular variant of a papillary thyroid carcinoma (T4aN0M0) in 2004. A total thyroidectomy was performed followed by RAI therapy (cumulative dose 450 mCi) and TSH suppression therapy. He underwent a coronary artery bypass graft in 2006 for three-vessel coronary artery disease. In 2007, the patient presented with local, pulmonary and bone metastases of his thyroid tumour. He was enrolled in the phase II study with sorafenib and received 400 mg twice daily. Due to complaints of grade 3 diarrhoea the dose was reduced to 200 mg twice daily. After six months, the patient showed a partial response and good tolerance of the sorafenib. Late 2009 he was hospitalised with a myocardial infarction followed by severe heart failure. Coronary angiography showed no

Figure 2. *F-FDG PET scan from patient A before (a) and after 4 weeks (b) of vemurafenib treatment*



Physiological 18F-FDG uptake in brain, bladder, liver and spleen; pathological uptake in osseous, pulmonary and lymph node metastases, and carcinomatous pleuritis prior to vemurafenib (a). After 4 weeks of treatment slight decrease of FDG accumulation in some metastases: the centre of the left lung, dorsobasal in the right lung and two mediastinal lymph nodes, no new FDG-avid lesions (b).

significant stenosis. Given the possible role of sorafenib in luxating coronary spasms and thereby myocardial infarction this treatment was discontinued. No other therapeutic options were available for his thyroid tumour and the patient was followed in the referral hospital. Upon inquiry, the patient received radiotherapy for a local recurrence in the neck in May 2013. At the end of 2013, he was in a reasonable condition with a relatively good quality of life.

Patient C is a 79-year-old female who underwent a subtotal left hemithyroidectomy in 1985 because of a 'follicular lesion', histologically diagnosed as a follicular adenoma. In 2003 she presented with a mass in the neck and lung metastasis. Revision of the pathological specimen from 1985 revealed a follicular thyroid carcinoma. The patient underwent a completion thyroidectomy. RAI therapy (450 mCi) was followed by surgical excision of three RAI refractory lung metastases. In 2005 she had recurrent disease in the neck and new lung metastases. Surgical re-exploration of the neck was followed by radiotherapy (70 Gy in 35 fractions). In 2009, the lung metastases became progressive and a new occipital skull metastasis was treated with radiotherapy (10x3 Gy). The patient declined systemic therapy. In August 2011, she presented with pain, based on an impending pathological fracture of the femoral neck. She underwent an hemiarthroplasty after embolisation. Once more the patient declined systemic treatment. At the end of 2013 she experienced no other limitations of her metastatic disease, except from blindness of her right eye due to a metastasis.

These cases demonstrate both the (long-term) benefits that can be achieved with targeted therapy (case A), the potential (severe) toxicity (case B) of these agents, and the slowly progressive course of metastatic differentiated thyroid carcinoma (DTC) (case C).

TARGETED THERAPIES

Preclinical studies have shown that inhibition of kinases that play a role in signalling pathways involved in thyroid tumours may lead to a decrease in tumour growth. Several of these kinase inhibitors have been investigated with encouraging results (*table 2 and 3*). Here we discuss the agents previously mentioned in our case presentations (*figure 1*).

Sorafenib (BAY 43-9006) is an orally active tyrosine kinase inhibitor (TKI) targeting BRAF, vascular endothelial growth factor receptor 1 and 2 and rearranged during transfection (RET), resulting in pro-apoptotic and antiangiogenic actions. Several phase II trials with sorafenib in patients with advanced DTC have been conducted, showing promising results.[4-6] In a recently performed phase III study, investigating the efficacy and safety of sorafenib in patients with advanced, RAI-refractory DTC, 417 patients were randomised between sorafenib twice daily 200 mg and placebo with the option of crossover in case of disease progression. The median progression-free survival in the placebo and sorafenib group was 5.8 months and 10.8 months respectively (HR 0.587; $p < 0.0001$).[7]

Everolimus (RAD001) is an orally available derivative of rapamycin that interferes with the regulation of cell cycling, cell growth and cell survival mechanisms through binding to the mammalian target of rapamycin. Recently published data of a phase II study of everolimus in patients with advanced thyroid cancer of all histological subtypes (n=38) reported a median PFS of 47 weeks.[8] Currently, a phase II study with everolimus in patients with unresectable or metastatic DTC, ATC and MTC is being conducted in the Netherlands. Results of this trial will be known at the end of 2014.

Vemurafenib (PLX 4032) is a TKI that specifically inhibits the BRAF V600E and V600K mutated kinases. Recent data of a phase II study in patients with a papillary thyroid carcinoma (PTC) reported a median progression-free survival of 15.6 and 6.8 months in treatment-naive patients and patients previously treated with a TKI, respectively.[9]

Although targeted therapies are better tolerated than cytotoxic chemotherapy, many patients develop side effects that require dose reduction or additional medication. The most common adverse events per targeted agent are summarised in *table 4*.

Table 2. *Summary of studies in thyroid cancer*

Drug	Tumour type	N	RR	SD	PFS	Referentie
Sorafenib	DTC	41 30 26 207	15% 23% 27% 12%	56% (≥24 weeks) 53% 58% 42% (≥26 weeks)	15 months 79 weeks 18 months 11 months	Kloos et al. 2009 Gupta et al. 2008 Schneider et al. 2012 Brose et al. 2013
Everolimus	All types	38	5%	45% (≥24 weeks)	47 weeks	Lim et al. 2013
Vemurafenib	DTC	3 51	33% 61%	66% -	12 months 16 months+ 7 months+	Kim et al. 2013 Brose et al. 2013
Motesanib	DTC+MTC DTC	71 93	7% 14%	49% (>12 weeks) 35% (>24 weeks)	- 40 weeks	Rosen et al. 2007 Sherman et al. 2008
Vandetanib	DTC	72	1%	56%	11 months	Leboulleux et al. 2009
Sunitinib	DTC	12 31	8% 13%	67% 68%	- -	Ravaud et al. 2009 Cohen et al. 2009
Thalidomide~	DTC+MTC	28	18%	32%	-	Ain et al. 2007
Gefitinib	All types	18	0%*	24% (>24 weeks)*	16 weeks*	Pennell et al. 2008
Pazopanib	DTC	37	32%	65%	12 months	Bible et al. 2009
Axitinib	DTC	45	31%	42%	18 months	Cohen et al. 2008
Lenalidomide	DTC	18	23%	45%	-	Ain et al. 2008

RR = response rate; SD = stable disease; PFS = progression free survival; DTC = differentiated thyroid cancer; MTC = medullary thyroid cancer; - not reported; + 15.6 months in the TKI naive group and 6.8 months in the group previously treated with a TKI, c-KIT stem cell factor receptor; TNFα = tumour necrosis factor alpha; * overall results; ° DTC+MTC results.

Table 3. *Kinase inhibitors and their targets*

Drug	Target(s)
Sorafenib	BRAF VEGFR 1,2 RET
Everolimus	mTOR
Vemurafenib	BRAF V600E
Motesanib	VEGFR 1-3 RET c-KIT
Vandetanib	VEGFR 2,3 RET EGFR
Sunitinib	VEGFR 1-3 RET RET/PTC 1-3
Thaliodomide*	VEGFR TNFα
Gefitinib	EGFR
Pazopanib	VEGFR 1-3 c-KIT
Axitinib	all VEGFRs
Lenalidomide*	VEGFR TNFα

*** exact mechanism of action unknown.**

DISCUSSION

Up to 50% of follicular and 12% of Hürthle cell malignancies contain RAS mutations.[10] The RAF proteins are cytoplasmic serine/ threonine protein kinases that are effected downstream by RAS. Of these, BRAF is the most efficient at phosphorylating mitogen-activated protein kinase (MAPK) and is important in proliferative as well as apoptotic pathways.[11] Point mutations leading to BRAF signalling independent of binding to RAS have been reported in 35-70% of PTCs, underlining the significance of the RAS/RAF/MAPK pathway in thyroid cancer.[12] BRAF is an important regulator of thyroid-specific protein expression and proliferation.[13] BRAF mutations are associated with recurrent and persistent disease, a higher rate of lymph node metastasis and a higher tumour-node metastasis stage.[14] In human thyroid cancer, BRAF V600E is associated with vascular endothelial growth factor overexpression, which in turn is associated with increasing tumour stage and invasiveness.[15]

Furthermore, BRAF is a putative downstream signal transducer for RET/PTC. A translocation of the RET/ PTC oncogene is seen in 25% of PTCs, resulting in the generation of chimeric oncogenes and proteins responsible for the initiation of tumour formation. Based on evidence that BRAF is involved in the development of PTC in the

Table 4. *Most common side effects (≥ 1/10 patients) per system organ class per targeted therapy*

System organ class	Sorafenib	Everolimus	Vemurafenib
General	Fatigue Headache	Fatigue Headache Fever Weight loss	Fatigue Headache Fever Anorexia
Blood and lymphatic system disorders	Lymphopenia	Anaemia Thrombocytopenia	
Cardiac disorders	Hypertension Bleeding	Peripheral oedema	Peripheral oedema
Respiratory disorders			Cough
Gastrointestinal disorders	Diarrhoea Nausea Vomiting	Diarrhoea Nausea Vomiting	Diarrhoea Nausea Vomiting Constipation
Musculoskeletal and connective tissue disorders			Myalgia Arthralgia Back pain
Skin disorders	Alopecia Rash HFS Erythema Pruritus	Mucositis Rash Pruritus Dry skin	Photophobia Rash Actinic keratosis Pruritus Erythema Dry skin Alopecia Hyperkeratosis
Laboratory disorders	Hypophosphataemia Elevated amylase Elevated lipase	Hypercholesterolaemia Hypertriglyceridaemia Hyperglycaemia	Elevated gammaGT
Neoplasms			SCC of the skin Seborrhoeic keratosis Skin papilloma

HFS = hand foot syndrome, SCC = squamous cell carcinoma.

progression of anaplastic carcinoma, BRAF is an attractive target in thyroid cancer.[16]

The AKT pathway plays an important role in cell proliferation and survival and has been found by others to be aberrantly activated in thyroid tumours.[17-20] An important player in this pathway is the PI3KCA subunit that in turn is also regulated by RAS. Activation of the PI3K/AKT pathway is seen in thyroid adenomas, follicular thyroid carcinomas and ATCs.

Since the knowledge of the biological basis of thyroid cancer has increased, systemic treatment options for metastatic DTC have changed. There are a wide variety of treatment strategies for patients with extensively metastasised thyroid cancer, although this type of cancer is rare and often has a slowly progressive course. The evidence for these different treatment strategies is limited. To date, only sorafenib is available as standard systemic treatment for patients with progressive, RAI-refractory disease. However, in case of slowly progressive disease, the side effects of systemic treatment outweigh the potential benefits. Therefore, patients must show at least progressive disease within 12-14 months before initiation of therapy based on the RECIST criteria.

Given the low incidence of (metastatic) thyroid carcinoma, its slowly progressive course and the potential toxicity of targeted therapies, the timing of initiation of therapy is a delicate issue. It is of great importance to take the natural course of disease into account and to value not only possible benefits but also toxicity before starting a targeted therapy. Hence, initiation of systemic therapy preferably has to be coordinated in a specialised centre and if possible to enrol patients in clinical studies in order to further determine the position of targeted therapies, to develop more effective (combination) treatment schemes, and above all, to identify those patients that truly benefit.

DISCLOSURES

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ORIGINAL ARTICLE

IP-10 in chronic hepatitis C patients treated with high-dose interferon

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ABSTRACT

Introduction: Interferon-γ-inducible protein-10 (IP-10) serum levels are associated with IL28B genotype and may predict response to interferon/ribavirin-based therapy in chronic hepatitis C patients. Our aim was to relate IP-10 levels before and during treatment to treatment outcome, viral HCV-RNA kinetics and IL28B genotype.

Patients and methods: A cohort of chronic hepatitis C patients was treated with high-dose interferon for six weeks, followed by standard peginterferon/ribavirin for 24 or 48 weeks. IP-10 and HCV-RNA levels were frequently determined before, during and after treatment.

Results: IP-10 levels increased from log2.56 pg/ml at baseline to log3.48 pg/ml at Day 1 and gradually diminished thereafter. IP-10 levels at any time point were not statistically different between patients with or without sustained viral response (SVR). Patients with IL28B CC genotype had significantly lower baseline IP-10 levels ($p = 0.019$) and a higher increase of IP-10 levels from baseline to Day 1 than patients with IL28B non-CC genotypes ($p = 0.015$). Patients with HCV-RNA decline $\geq 2.28\log_{10}$ at Day 1 had significantly lower baseline IP-10 levels ($p = 0.016$) and a higher increase of IP-10 levels from baseline to Day1 ($p = 0.047$) than patients with HCV-RNA decline of $< 2.28\log_{10}$ at Day 1.

Conclusions: In patients treated with high induction dose interferon, IP-10 levels at any time point were not predictive for SVR. Low baseline IP-10 levels and a higher increase of IP-10 levels from baseline to Day 1 were associated with IL28B CC genotype and HCV-RNA decline $\geq 2.28\log_{10}$ at Day 1. This suggests that, in our cohort, for prediction of SVR the added value of IP-10 to IL28B genotype and early viral kinetics is limited.

KEYWORDS

HCV, IL28B, interferon-based therapy, interferon-gamma-inducible protein-10, IP-10

INTRODUCTION

Hepatitis C virus (HCV) infection is a leading cause of chronic hepatitis affecting over 170 million people worldwide.[1] After being exposed to HCV, a chronic infection develops in approximately 80% of cases.[2] Chronic hepatitis C (CHC) is characterised by liver inflammation due to pro-inflammatory cytokines and infiltration of specific and non-specific T lymphocytes.[2] The damage inflicted leads to liver fibrosis and may ultimately cause liver cirrhosis, hepatocellular carcinoma and death.[3]

After an infection with HCV the innate immune system initiates a nonspecific immune response through type I interferon, leading to the activation of the intracellular pathway resulting in the induction of multiple interferon-stimulated genes (ISGs). Type I interferon has also immunomodulatory effects by activating and modulating the function of different kinds of leukocytes, including natural killer (NK) cells, macrophages, dendritic cells and T lymphocytes. This results in a strong specific CD4+/CD8+ T-cell response leading ideally to the clearance of HCV.[4] In most cases, however, a chronic HCV infection is established, in which the HCV-specific immune responses are weaker and less specific than in acute-resolving HCV infection.[5]

The gene encoding the non-ELR CXC chemokine interferon-γ-inducible protein-10 (IP-10 or CXCL10) is an ISG that is induced by interferon-γ and tumour necrosis factor alpha. It is produced by different kinds of cells such as endothelial cells, fibroblasts, mesangial cells, monocytes, neutrophils and hepatocytes. After binding to its receptor CXCR3, IP-10 functions as a chemotactic cytokine for T lymphocytes, monocytes and NK cells and induces adhesion of activated memory/effector T cells.[6] Levels of IP-10 are higher in patients with chronic HCV infection than in healthy controls.[7]

Multiple inflammatory chemokines and cytokines have been suggested as markers for treatment outcome because of their regulatory function in the HCV-specific immune response. Most of these cytokines are modulated by

exogenous interferon and play a critical role in viral clearance.[8] In patients who develop a sustained viral response (SVR) after interferon-based therapy, the baseline activation of the immune system tends to be lower prior to treatment than in patients who do not achieve SVR.[8-10] This difference of baseline activation of the immune system might be influenced by single nucleotide polymorphisms (SNPs) on chromosome 19 near the interleukin-28B gene (IL28B), encoding interferon-λ. IL28B gene polymorphisms are highly associated with treatment outcome in CHC patients treated with interferon-based therapy.[11] Most data have been published on two of these gene polymorphisms, SNPs rs12979860 and rs8099917, associated with SVR after peginterferon and ribavirin therapy.[12,13]

Baseline IP-10 levels may be a prognostic marker for the outcome of interferon-based therapy in HCV infection.[14-23] There are several studies that describe a relation between low baseline IP-10 levels and higher rates of rapid viral response (RVR, HCV-RNA undetectable after four weeks of treatment)[14,15,20,23] and SVR after treatment with peginterferon and ribavirin.[14-22] However, whether the IP-10 level really is a predictor for SVR and/or RVR remains a subject of discussion.

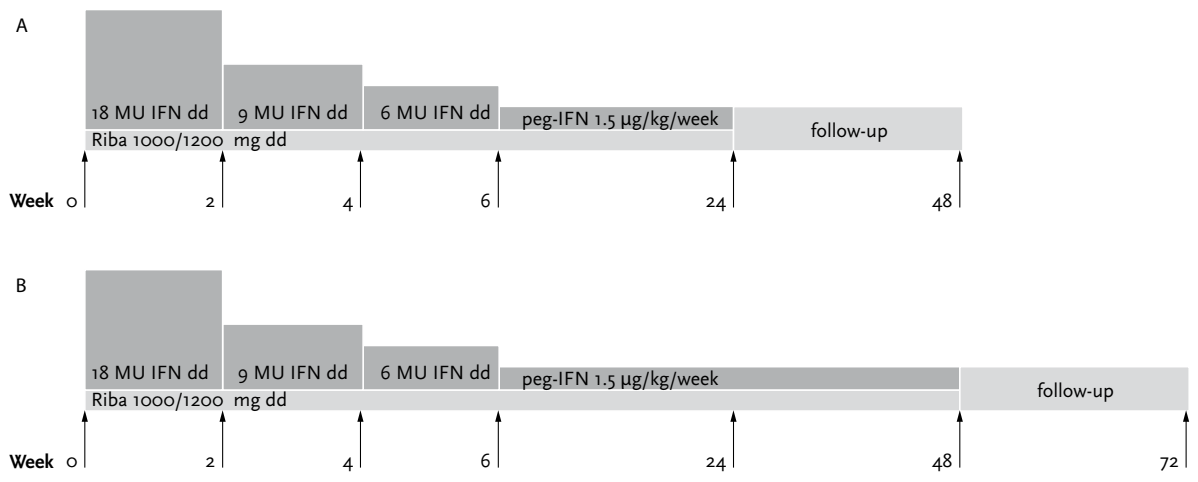
From 2002-2005 a cohort of CHC patients (treatment-naive patients with HCV genotype 1 or 4 and patients of all genotypes with failure to respond to interferon-based therapy) was treated with a high induction dose of interferon combined with ribavirin, followed by peginterferon and ribavirin.[24] Our aim was to investigate, in this cohort of patients, whether IP-10 levels before and during treatment with this high dose of interferon were related to treatment outcome, IL28B genotype and HCV-RNA kinetics.

PATIENTS AND METHODS

Patients and treatment regimen

From 2002-2005, a cohort study was performed in which 100 CHC patients were included (treatment-naive patients with HCV genotype 1 or 4 and patients of all genotypes who failed previous therapy with either classical interferon alone, or a combination of (peg)interferon and ribavirin). The results of this study were reported in 2008.[24] All patients were treated for six weeks with high-dose interferon-alpha 2b (Merck Pharmaceuticals, USA), combined with ribavirin (weight-based: 1000 mg/day in patients weighing < 75 kg, and 1200 mg/day in patients weighing > 75 kg), followed by 24 or 48 weeks of peginterferon alpha 2b (1.5 µg/kg once a week) and ribavirin (weight-based 1000-1200 mg/day). All patients were also treated with amantadine hydrochloride 200 mg/day (Symmetrel®, Novartis, Basel, Switzerland). *Figure 1* describes the study design. During the first six weeks of treatment the following interferon-induction regimen was used: Weeks 1 and 2: 18 MU/ day in three divided doses; Weeks 3 and 4: 9 MU/day in three divided doses; Weeks 5 and 6: 6 MU/day in two divided doses. Patients with a decline in HCV-RNA ≥ $3\log_{10}$ at Week 4 (and transcription-

Figure 1. *Study design.[24] Patients with a decline in HCV-RNA ≥ $3\log_{10}$ at Week 4 (and TMA undetectable at Week 24) were randomised to stop treatment at 24 weeks (A) or to continue to 48 weeks (B). Patients with a decline in HCV-RNA < $3\log_{10}$ at Week 4 were treated for 48 weeks (B). Treatment was stopped in all patients with detectable HCV-RNA at Week 24 (A). All patients were followed for 24 weeks after completion of therapy*



HCV = hepatitis C virus; IFN = interferon-alpha-2b; Riba = ribavirin.

mediated amplification (TMA) undetectable at Week 24) were randomised to stop treatment at 24 weeks or to continue to 48 weeks. Patients with a decline in HCV-RNA < $3\log_{10}$ at Week 4 were treated for 48 weeks. Treatment was stopped in all patients with detectable HCV-RNA at Week 24. All patients were followed for 24 weeks after completion of therapy.

Plasma samples were stored at -80 °C at baseline, Days 1 and 3, Weeks 1, 2, 3, 4, 6, 8, every 4 weeks until the end of treatment, and after cessation at Weeks 4, 12 and 24. The study was approved by the institutional review board. Written informed consent was obtained from each patient.

Patient and sample selection for measurements

All patients who completed the whole treatment course or who had to stop treatment before Week 24 or 48 because of exclusion criteria were included in our study to determine IL28B genotype and to measure IP-10 and HCV-RNA levels at baseline, Day 1, Weeks 1, 2, 4 and 6, at end of treatment and at end of follow-up. Patients who stopped treatment prematurely (dropouts) between Day 0 and Week 24 (for other reasons than the above-mentioned exclusion criteria), and patients for whom baseline plasma samples were not available were excluded. Of the 100 included patients in the original study, 85 patients were included in this study. Reasons for exclusion of the remaining 15 patients were dropout due to side effects of the treatment (n = 12), dropout because of non-medical reasons (n = 1), and lack of available plasma samples (n = 2). From six of the included 85 patients Day 1 plasma samples were missing. For that reason, change in IP-10 levels from baseline to Day 1 could not be calculated and therefore these patients were excluded.

HCV-RNA measurement

HCV-RNA was quantitatively measured using a bDNA assay (VERSANT® HCV 3.0 assay; Siemens, Germany); linear dynamic range 6.15 x 10^2 to 7.7 x 10^6 IU/ml).[25] A qualitative HCV-RNA measurement was performed when the quantitative test was negative, using TMA (VERSANT® HCV qualitative assay, Siemens, Germany; lower limit of detection (LLD) 5 IU/ml).[26] HCV genotypes were determined using the TruGene® HCV genotyping assay and the Open-Gene® automated DNA sequencing system (Bayer Diagnostics, Berkeley, California, USA).

IP-10 measurement

IP-10 levels were measured using a solid base sandwich ELISA (lower limit of detection 4.46 pg/ml, dynamic quantitative assay range 7.8-500 pg/ml; Quantikine human CXCL10/IP-10 immunoassay, R&D Systems). Plasma samples were tested in duplicate in a dilution of 1:5 (according to the manufacturer's description). A first evaluation of the test results showed that in many cases IP-10 levels, especially at Day 1, were above the upper limit of the assay range of 500 pg/ml. By using Bland-Altmann plots comparing duplicate measurements, we retested all plasma samples with an initial test value > 730 pg/ml (with 1:5 dilution) after a second dilution step of 1:5, resulting in a dilution of 1:25 for calculation of IP-10 levels.

IL28B genotyping

IL28B single nucleotide polymorphism (SNP) genotyping (rs12979860) was performed by High Resolution Melting Curve Analysis (HRMCA) on a LightCycler480 (Roche Applied Science) using custom-designed primers and LC480 High Resolution Melting Master (Roche Applied Science). Results were analysed with the LC480 HRMCA module implemented in the LC480 Software.

Assessment of treatment outcome

The following definitions were used to categorise treatment outcomes:

SVR: Undetectable HCV-RNA at the end of follow-up (24 weeks after end of treatment); RVR: Undetectable HCV-RNA at week 4 during treatment; Non-response: Detectable HCV-RNA (TMA positive) at all time-points during treatment and at end of follow-up; Relapse: Undetectable HCV-RNA (TMA negative) at end of treatment but detectable HCV-RNA at end of follow-up; Non-SVR: All patients who did not achieve SVR. Dropout: Any patients who stopped treatment prematurely between Day 0 and Week 24/48 or who were lost to follow-up during the 24 weeks thereafter.

Statistical analysis

IP-10 values were logarithmically transformed to achieve a normal distribution. Graphic representation was performed using Graphpad Prism version 5 for Windows (GraphPad Software, San Diego, California, USA) and SPSS version 19.2 for Windows (SPSS Inc., Chicago, Illinois, USA). Data were analysed on per protocol basis. We used the Bland-Altmann plots, Student's t-test, the Mann-Whitney U-test, chi-square and Fisher's exact test where appropriate. Differences were considered statistically significant when p was < 0.05. A receiver operating characteristic (ROC) analysis was performed to determine which level of HCV-RNA decline gave the best prediction for SVR at Day 1.

RESULTS

Baseline characteristics and treatment outcome

Baseline characteristics of the 85 patients included in the study are shown in *table 1*. Thirty-six of the 85 patients (42%) achieved SVR, whereas 49 (58%) did not. Treatment-naive patients, patients with RVR, IL28B CC genotype or a low METAVIR fibrosis stage (F0-F1-F2)

Table 1. *Baseline characteristics of patients treated with high-dose induction interferon followed by peginterferon and ribavirin for 24 or 48 weeks according to SVR*

	SVR	Non-SVR	p-values
N (%)	36 (42)	49 (58)	
Male (%)/ female (%)	28 (33)/ 8 (9)	38 (46)/ 11 (13)	0.98
Mean age, years (range)	44 (25 – 63)	46 (19 – 67)	0.37
Baseline HCV-RNA (log)	5.97	5.77	0.28
Naive / non-naive (%) *	24 (28)/ 12 (14)	22 (26)/ 27 (32)	0.046
Genotype (%)			
1	23 (27)	34 (40)	0.65
4	6 (7)	12 (14)	0.43
2/3/5	7 (8)	3 (4)	0.09
RVR / non-RVR (%)	19 (22)/ 17 (20)	5 (6) / 44 (52)	< 0.001
IL28B genotype CC / non-CC (%)	17 (20) / 19 (23)	9 (11) / 40 (47)	0.008
Baseline IP-10 (log pg/ml) (±SEM)	2.53 (0.04)	2.59 (0.05)	0.34
Liver biopsy (%)	32 (41)	46 (59)	
Fibrosis stage Metavir F3/F4 (%)	12 (15)	31 (40)	0.001

*** Non-naive: earlier treatment with either classical interferon alone, or combination therapy with (peg)interferon and ribavirin.**

were significantly more likely to achieve SVR. The group of patients with genotype 2, 3 or 5 had a higher SVR rate than patients with genotype 1 or 4. Statistically this was not significant, but there was a trend (p = 0.09). IP-10 levels at baseline were lower in patients with SVR compared with patients without SVR, but this difference was not statistically significant (*table 1*). There was no statistically significant difference in baseline IP-10 levels between patients with a partial response or patients with no response (data not shown). There were 26 patients with IL28B genotype CC of which 17 (65%) had SVR and 9 (35%) did not. Of the 59 IL28B non-CC genotype patients 19 (32%) had SVR (p = 0.008) (*table 1*). A cut-off of < / ≥ 600 pg/ml was used (chosen based on earlier literature[16]) to define high and low IP-10 levels at baseline. In the group of patients with baseline IP-10 levels ≥ 600 pg/ml treatment-experienced patients had lower SVR rates that treatment-naive patients. However, these differences were not statistically significant (*table 2*).

Table 3. *Baseline IP-10 levels and various response parameters*

	Baseline IP-10 levels (mean log ± SEM, pg/ml)	p-value	
Naive / non-naive	2.54 (0.05)	2.59 (0.04)	0.51
Genotype 1 / Genotype non-1	2.60 (0.04)	2.50 (0.04)	0.098
Baseline HCV-RNA < 600,000 / ≥ 600,000 IU/ml	2.57 (0.05)	2.56 (0.04)	0.81
Fibrosis score Metavir F3-F4 / F0-F2	2.56 (0.04)	2.58 (0.05)	0.81
IL28B genotype CC / non-CC	2.45 (0.05)	2.62 (0.04)	0.019
RVR / non-RVR	2.44 (0.05)	2.61 (0.04)	0.016

Baseline IP-10 levels and response parameters

Mean log IP-10 levels at baseline were significantly lower in patients achieving RVR than in patients without RVR (2.43 pg/ml / 2.62 pg/ml, p = 0.016) (*table 3*). This was also the case in patients with IL28B CC genotype versus patients with IL28B non-CC genotypes (2.45 pg/ml / 2.62 pg/ml, p = 0.019) (*table 3*). Statistically there was a trend towards lower baseline mean log IP-10 levels in HCV genotype non-1 patients (compared with HCV genotype 1 patients, p = 0.098) (*table 3*). For all other parameters shown in *table 3* there was no statistically significant difference in baseline IP-10 levels. Because it is well known that IP-10 levels and IL28B

Table 2. *SVR versus non-SVR in naive and treatment-experienced patients with baseline IP-10 levels of < or ≥ 600 pg/ml*

	IP-10 baseline (pg/ml)				
	< 600 pg/ml		≥ 600 pg/ml		
	Naive	Non-naive	Naive	Non-naive	Total
SVR, n/total (%)	19/38 (50)	10/32 (31)	5/8 (63)	2/7 (29)	36/85 (42)
Non-SVR, n/total (%)	19/38 (50)	22/32 (69)	3/8 (37)	5/7 (71)	49/85 (58)
Total, n/total (%)	38/70 (54)	32/70 (46)	8/15 (53)	7/15 (47)	

are related, we performed a multivariate analysis showing that IL28B CC genotype was an independent predictor of RVR (*table 4*). This multivariate analysis showed a trend towards lower baseline IP-10 levels in patients achieving RVR (p = 0.079).

IP-10 levels during therapy

From baseline to Day 1 an almost tenfold increase of mean log IP-10 levels was observed (from log 2.56 pg/ml to log 3.48 pg/ml) (*figure 2*). The range of the fold increase in IP-10 levels was 2-40. The increase was related to baseline IP-10 levels: the lower the baseline IP-10 levels, the greater the increase at Day 1 (*table 5*).

Thereafter, mean log IP-10 levels diminished gradually, returning to baseline levels between Week 4 and 6 of treatment, and diminishing further to a level significantly lower than the baseline level at end of treatment (2.41 pg/ml, p = 0.01) and the end of follow-up (2.35 pg/ml, p = 0.01) (*figure 2*).

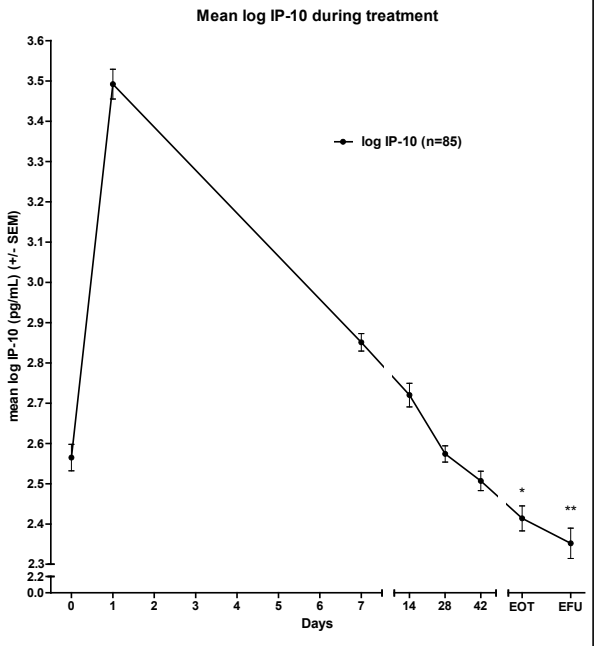
IP-10 levels during therapy and treatment outcome

Before and during treatment mean log IP-10 values were in general lower in SVR patients than in non-SVR patients, but this difference was not statistically significant at any time point (*figure 3*). At end of follow-up, mean log IP-10

Table 4. *Predictors of RVR: multivariate analysis of baseline IP-10 levels and IL28B genotype*

	RVR	Non-RVR	Confidence interval (95%)	p-value
IL28B genotype CC, N (%)	14 (58)	12 (20)	0.78 – 0.65	0.006
Non-CC, N (%)	*10 (42)*	*49 (80)*		
Log IP-10 baseline (mean, pg/ml)	2.44	2.61	0.013 – 1.267	0.079
Total, N (%)	24 (28)	61 (72)		

Figure 2. *IP-10 levels before and during treatment. A 1log$_{10}$ rise at Day 1 was observed, and thereafter IP-10 levels gradually declined and were significantly lower than baseline levels at end of treatment (EOT) and end of follow-up (EFU)*

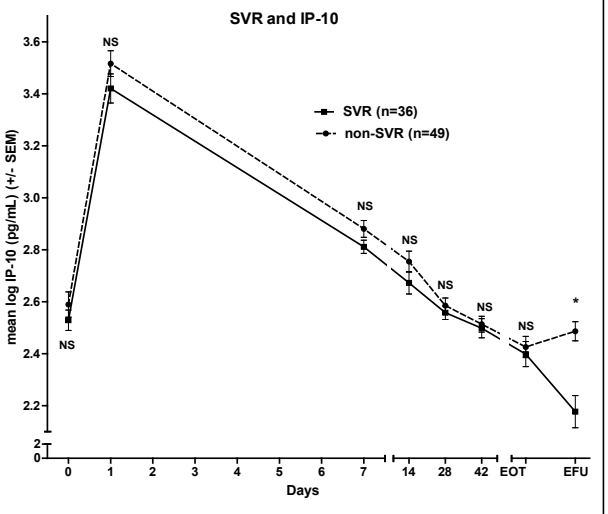


* p = 0.01 ** p = 0.01.

Table 5. *Factor of increase in IP-10 levels from baseline to Day 1, different baseline IP-10 levels (dependent on the baseline IP-10 level: the lower the baseline IP-10 level, the higher the factor of increase)*

IP-10 baseline	N	Factor of increase D1 (mean)	p-value
< 150 ≥ 150	8 71	27 10	0.005
< 300 ≥ 300	31 48	16 9	0.001
< 375 ≥ 375	41 38	15 8	< 0.001
< 600 ≥ 600	68 11	13 4	< 0.001

Figure 3. *IP-10 levels before and during treatment: SVR versus non-SVR*



EOT at 24 Weeks (n = 55) or 48 Weeks (n = 30); EFU at 24 Weeks after EOT (n = 85).
*** p <0.001**

levels were significantly lower in patients with SVR than in non-SVR patients (2.40 pg/ml vs. 2.43 pg/ml, p < 0.0001) (*figure 3*).

IP-10 levels and HCV-RNA kinetics during therapy

A ROC curve (*figure 4*) was made to determine at which level of HCV-RNA decline at Day 1 prediction for SVR was optimal. This curve showed the best diagnostic odds ratio of 8.24 with a confidence interval of ± 1.04, corresponding with an HCV-RNA decline of ≥ 2.28$\log_{10}$, with a sensitivity of 58.3% and a specificity of 85.7% (*table 6*).

In 28 (33%) of the 85 included patients, the decline of HCV-RNA at Day 1 was ≥ 2.28$\log_{10}$, and in 57 (67%) it was not. In patients with an HCV-RNA decline of ≥ 2.28$\log_{10}$ or < 2.28$\log_{10}$ at Day 1 the baseline mean log IP-10 level was 2.45 pg/ml, and 2.62 pg/ml respectively (p = 0.016). At Day 1, IP-10 levels were slightly higher in patients with an HCV-RNA decline of ≥ 2.28$\log_{10}$ at Day 1 than in patients with a decline of < 2.28$\log_{10}$ at Day 1 (log3.51 pg/ml vs. log3.48 pg/ml), but this difference was not statistically significant (*table 7*). The increase of IP-10 levels from baseline to Day 1 was larger in patients with an HCV-RNA decline of ≥ 2.28$\log_{10}$ than in patients who did not show this decline (log1.09 pg/ml vs. log0.88 pg/ml, p = 0.047) (*table 7*).

IP-10 levels during therapy and IL28B genotype

The increase of IP-10 levels from baseline to Day 1 was significantly greater in patients with IL28B CC genotype than in patients with IL28B non-CC genotypes (log1.07 pg/ml vs. log0.89 pg/ml, p = 0.015) (*table 7*).

DISCUSSION

In contrast to what has been described earlier,[14-22,27] we did not find a clear association between IP-10 levels before or during treatment and SVR or non-SVR. There are also other studies that, like ours, did not confirm the association between a low baseline IP-10 level and SVR.[28-30] Nevertheless, in our study baseline IP-10 levels were significantly lower in patients with RVR than in those without RVR. The association of RVR and low baseline IP-10 levels without a significant difference in baseline IP-10 between SVR and non-SVR patients was previously described in HCV genotype 1 and 4 patients and in patients with acute HCV infection.[14,20,31] However, there are reports contradicting these findings, in which no difference was seen in baseline IP-10 levels between CHC patients with or without RVR[18,32] or with or without SVR.[28,33]

We also found a clear relation between IL28B genotype and SVR, in line with previous data.[11,13-15]

Figure 4. *ROC curve for the prediction of SVR on the basis of the HCV-RNA decline at Day 1. Best diagnostic test performance at a decline of HCV-RNA of ≥ 2.28$\log_{10}$ at Day 1. Diagnostic odds ratio 8.24 (CI ± 1.04). Sensitivity 58.3% and specificity 86.7%*

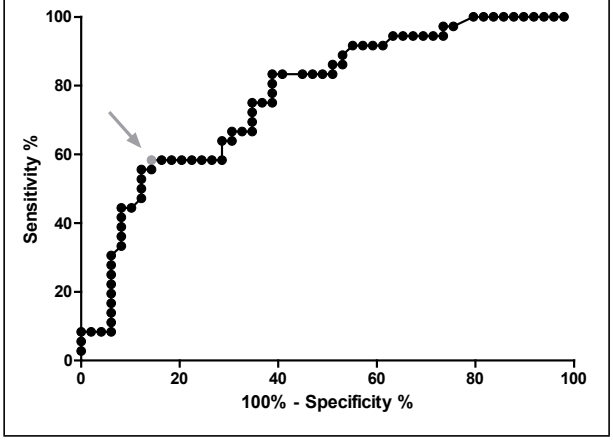


Table 6. *Patients with a decline of HCV-RNA at Day 1 of ≥ or < 2.28$\log_{10}$ and SVR or non-SVR status.*

Decline HCV-RNA Day 1	SVR (N)	Non-SVR (N)	Total	
≥ 2.28 $\log_{10}$	21	7	28	PPV 75.0%
< 2.28 $\log_{10}$	15	42	57	NPV 73.7%
Total	36	49	85	
	Sens 58.3%	Spec 85.7%		

PPV = positive predictive value; NPV = negative predictive value; Sens = sensitivity; Spec = specificity.

Table 7. *Increase of IP-10 levels from baseline to Day 1 after start of treatment according to different response parameters*

	IP-10 levels (mean log, pg/ml)		
	Baseline	**Day 1**	**Δ To-D1 (p-value)**
SVR / non-SVR	2.52 / 2.59	3.42 / 3.52	0.93 / 0.96 (p = 0.75)
RVR / non-RVR	2.44 / 2.61	3.47 / 3.50	1.03 / 0.91 (p = 0.19)
D1 HCV-RNA decline ≥2.28$\log_{10}$ / < 2.28$\log_{10}$	2.45 / 2.62	3.51 / 3.48	1.07 / 0.89 (p = 0.047)
IL28B genotype CC / non-CC	2.45 / 2.62	3.54 / 3.47	1.09 / 0.88 (p = 0.015)

Δ To-D1 = Difference between IP-10 levels from baseline to Day 1 after start of treatment.

A possible explanation for the relationship we observed between baseline IP-10 levels and RVR and the absence of a relationship between baseline IP-10 levels and SVR may be that the high induction dose of interferon resulted in a higher rate of RVR than would have occurred with a standard dose of IFN. Consequently, this higher rate of RVR with high induction IFN may not have the same predictive value for SVR as with standard (peg)IFN. It may also be that our cohort of patients was too small to show a statistical difference in baseline IP-10 levels and a change in IP-10 levels during treatment between patients achieving SVR or not. In multivariate analysis the association we found between low baseline IP-10 levels and RVR seemed to be dependent on IL28B CC genotype, where IL28B CC genotype was an independent predictor of RVR. This suggests that IL28B genotype is a more important factor for prediction of RVR (and SVR) than baseline IP-10 levels.

Our findings, demonstrating a relation between IL28B genotype and IP-10 levels, confirm the results of earlier studies, showing that patients with favourable IL28B polymorphisms (CC) had lower pre-treatment IP-10 levels than patients with unfavourable IL28B genotypes (CT or TT).[12,14,15,23,34] These studies also showed that when pre-treatment IP-10 levels are low (< 600 pg/ml), the predictive value for RVR or SVR of IL28B genotype is increased (especially in patients with CT and TT genotypes). These findings,[14-16] together with ours, implicate the utility of combining these two markers in predicting treatment outcome. Also in patients with acute HCV infection low serum IP-10 levels increased the predictive value of IL28B polymorphisms (SNPs rs12979860 and rs8099917) with regards to the spontaneous clearance of HCV.[35]

Treatment-experienced patients had a lower SVR rate than treatment-naive patients. In patients with a baseline IP-10 level of ≥ 600 pg/ml SVR rate was lower than in patients with a baseline IP-10 level of < 600 pg/ml, especially in treatment-experienced patients. These differences were not statistically significant, but the numbers were very small (n = 13). These findings confirm, what was already known, that treatment-experienced patients were less interferon responsive than naive patients. The higher dose of interferon did not overcome this lack of response. The fact that we did not find a relation between baseline IP-10 levels and SVR, and the fact that in this cohort of patients SVR rates were not higher than SVR rates of comparable cohorts of patients treated with standard peginterferon and ribavirin therapy, as described in literature,[36-40] supports this.

Our study is the first to describe IP-10 kinetics in CHC patients treated with high-dose interferon and amantadine. We found an almost tenfold increase of IP-10 levels at Day 1 after the start of treatment, which was dependent of baseline IP-10 levels (fourfold when baseline IP-10 level was ≥ 600 pg/ml to 27-fold when baseline IP-10 level < 150 pg/ml). A rise in IP-10 levels dependent of baseline IP-10 levels shortly (24 hours) after the start of treatment with peginterferon and ribavirin was also described in HCV/HIV co-infected patients.[32] In this study a threefold rise was seen in patients with a baseline IP-10 level of > 600 pg/ml versus a ninefold rise in patients with a baseline IP-10 level of < 150 pg/ml. Another study showed a dose-dependent two- to five-fold rise in IP-10 level, two days after the start of a low dose versus a normal dose of peginterferon in CHC patients.[30] As interferon upregulates ISGs, including IP-10, one may expect that the IP-10 expression induced after a high dose of interferon is greater than after a lower dose. Our data support this suggestion, and it may be that high-dose interferon induces such a high level of IP-10 expression that other factors such as the baseline IP-10 level are less important as a predictor for RVR and SVR.

We also found that, after the initial rise of IP-10 levels, the levels gradually decreased to below the baseline value at the end of treatment and at end of follow-up, and were significantly lower in patients achieving SVR. This has previously been described,[20-22,28] and may indicate that when HCV-RNA levels are declining, IP-10 is down-regulated.

It is unlikely that the addition of amantadine to the treatment regimen of our cohort of patients influenced SVR and IP-10 levels, since SVR rates were not different in patients with or without addition of amantadine, as was shown in several studies.[41,42]

In our study, a first phase viral decline (HCV-RNA decline of ≥ 2.28$\log_{10}$ at Day 1) was associated with lower baseline IP-10 levels, which is supported by earlier studies.[18,32] One of these studies showed that a first phase decline of HCV-RNA of > 1$\log_{10}$ at Day 1 of treatment with peginterferon/ribavirin was associated with lower IP-10 levels at baseline.[18] In HIV/HCV co-infected patients a similar pattern has been described, with a negative correlation between baseline IP-10 levels and the degree of HCV-RNA decline at Day 2 of treatment with peginterferon/ribavirin.[32] In contrast to earlier experience with interferon-based therapy, one study with peginterferon monotherapy combined with danoprevir showed that baseline IP-10 levels were positively correlated with a decline of HCV-RNA at Day 1 of treatment and that IP-10 levels at Day 7 and Day 14 were significantly lower than at baseline.[35] The association we found between this large first phase decline of HCV-RNA ≥ 2.28$\log_{10}$ and a significantly higher increase of IP-10 levels from baseline to Day 1 of treatment has not been described before. This may be due to the high induction dose of interferon applied in our study, inducing strong upregulation of ISGs responsible for a rapid decline of HCV-RNA. Our finding that the increase of IP-10 levels from baseline to Day 1

was larger in patients with IL28B CC genotype than in IL28B non-CC patients, suggests that induction of IP-10 is dependent of the IL28B genotype. This is also supported by our findings in multivariate analysis, where IL28B CC genotype was an independent predictor of RVR, but baseline IP-10 level was not.

A limitation to our study is the fact that our data are valid for patients with HCV genotype 1 and 4 because only limited numbers of patients with genotype 2, 3 and 5 were included in our study.

In conclusion, there was no significant difference in IP-10 levels between patients with or without SVR, but baseline IP-10 level was significantly lower in patients with RVR versus non-RVR. IP-10 levels changed markedly after one day of treatment with high induction dose interferon. The factor of increase of IP-10 levels from baseline to Day 1 was higher when the baseline IP-10 level was lower. There was a clear relation between IP-10 levels at baseline and Day 1 of treatment and a decline of HCV-RNA of $\geq 2.28\log_{10}$ at Day 1. Baseline and dynamic IP-10 levels early during treatment seem to be closely related to early viral kinetics and IL28B genotype. At present an all-oral direct-acting antiviral (DAA) combination treatment will result in eradication of HCV in most patients, and predictive markers for response become of less importance. However, in the future some patients such as those with HCV genotype 3 and some difficult-to-treat patients such as those with end-stage liver cirrhosis will fail to achieve SVR. Immunological markers may help to understand why some patients also fail on DAA therapy.

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Najaarscongres Nederlandse Vereniging voor Gastroenterologie (NVGE), October 3-4 2013. Oral Presentation at Meeting Nederlandse Vereniging voor Hepatologie, (October 4). S.B. Willemse, H.C. Gelderblom, R. Rientsma, R. Molenkamp, H.W. Reesink, J. Schinkel. Dynamic changes in IP10 level during interferon therapy: association with IL28B genotype and early viral kinetics.

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ORIGINAL ARTICLE

Determinants of health-related quality of life in older patients after acute hospitalisation

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ABSTRACT

Background: To assess the association between demographics, comorbidity, geriatric conditions, and three health-related quality of life (HRQOL) outcomes one year after acute hospitalisation in older patients.

Methods: A prospective cohort study conducted between 2006 and 2009 with one-year follow-up in 11 medical wards at two university hospitals and one teaching hospital in the Netherlands. Participants were 473 patients of 65 years and older, acutely hospitalised for more than 48 hours.

Demographics, Charlson Comorbidity Index (CCI), and data on 18 geriatric conditions were collected at baseline. At baseline and 12 months post-admission, the EuroQol-5D was administered. Based on a population-derived valuation (Dutch EuroQol-5D tariff), utilities (range -0.38–1.00) were determined, which were used to calculate quality-adjusted life years (QALY) over one year (max QALY score 1). The EuroQol-5D visual analogue scale (VAS) (range 0-100) was also used. Linear regression analyses were performed to explore the association between the independent variables and the three HRQOL outcomes.

Results: CCI was most consistently significantly associated with HRQOL outcomes: Beta -0.05 (95% CI -0.06–-0.03) for utility, -0.04 (95% CI -0.05-0.03) for QALY, -1.03 (95% CI -2.06-0.00) for VAS, $p < 0.001$, < 0.001, 0.05, respectively). Baseline utility was significantly associated with one-year utility (beta 0.25, 95% CI 0.11-0.39, $p < 0.01$) and QALY (beta 0.31, 95% CI 0.17-0.45, $p < 0.001$). The number of geriatric conditions at baseline was more strongly associated with one-year utility than any individual geriatric condition.

Conclusion: Less comorbidity, better utility and less geriatric conditions at baseline were associated with better HRQOL one year after acute hospitalisation in older patients.

KEYWORDS

Aged, aged 80 and over, geriatric assessment, HRQOL, quality of life

INTRODUCTION

In older patients, the acute illness leading to hospitalisation is often accompanied by geriatric conditions such as impairment in activities of daily living, cognitive impairment, delirium, falls, and malnutrition.[1] Moreover, during hospitalisation older people often experience increased dependence.[2] The prognosis of patients aged 65 years and older after hospitalisation is poor: three months after acute admission, 20-30% of them have died, and of those still alive, 30% have persistent functional impairment.[1,3]

Health-related quality of life (HRQOL) is an important indicator of a patient's well-being. HRQOL can be defined in multiple ways, but there is agreement that HRQOL is the functional effect of a medical condition and/or its treatment upon a patient's physical, social, and emotional well-being (quality of life).[4,5] Research has shown that factors associated with HRQOL in older adults can be divided into three categories. First, demographic factors such as higher age, female sex and lower education levels are associated with decreased HRQOL.[6] Secondly, factors related to a patient's disease burden, such as specific diseases and therapy,[4-8] higher self-rated disease severity[7] and a higher number of chronic conditions[9] are associated with decreased HRQOL. Thirdly, geriatric conditions including polypharmacy,[10] falls,[11] cognitive and functional impairment,[8,10,12] are associated with decreased HRQOL in community-dwelling older adults.

However, it is unclear to what extent these factors are associated with HRQOL in acutely admitted older hospital patients. Therefore, we aimed to explore the association between these factors and HRQOL outcomes (expressed in utility, visual analogue scale (VAS) and quality-adjusted life years (QALY)) in older patients, one year after acute hospitalisation.

METHODS

Design and setting

This study was part of a multicentre prospective cohort study of acutely admitted older patients, the DEFENCE study (Develop strategies Enabling Frail Elderly New Complications to Evade). The methods of this study (design and setting, patients, data collection and follow-up) were reported in detail by Buurman *et al.*[13] Briefly, DEFENCE was conducted between 2006 and 2009 in three hospitals in the Netherlands: the Academic Medical Center in Amsterdam; the University Medical Center Utrecht in Utrecht; and the Spaarne Hospital in Hoofddorp. Patients were recruited from general medical wards. All hospitals had a geriatric consultation team. The medical ethics committees of all hospitals approved the study.

Study participants

All consecutive patients aged 65 years and older, who were acutely admitted to one of the participating wards and hospitalised for at least 48 hours, were enrolled (n = 639). The analytic sample for this substudy included patients with a Mini Mental State Examination (MMSE) score of 16 and higher, because people with lower scores were considered unable to complete the EuroQol-5D (EQ-5D).[14,15] Of the 639 DEFENCE participants, 104 (13.7%) had an MMSE score below 16 and were excluded from this substudy. For an extra 62 (9.7%) DEFENCE participants (complete) EQ-5D scores were not available at baseline. In 12.9%, this was due to a delirium at admission or fatigue at the end of the Comprehensive Geriatric Assessment (CGA). In 87.1% this was due to the DEFENCE protocol that stated that a full CGA was not to be administered on odd days. Thus, the total analytical sample included 473 patients.

Data collection

After written informed consent was obtained, trained geriatric research nurses administered the CGA to the patient and the patient's primary informal caregiver within 48 hours of admission. Data were also extracted from the medical records. Follow-up data were collected at three and 12 months after hospital admission. For follow-up, the municipal data registry was checked to determine whether participants were still alive. Subsequently, follow-up information was collected from living participants and their proxy by telephone. When applicable, we tried to retrieve the date of death from the hospital registry, municipal data registry and/or proxy.

Health-related quality of life outcomes

We evaluated three HRQOL outcomes based on the EQ-5D:[15] utility, QALY, and VAS score one year after admission. The research nurse administered the EQ-5D to the patient during the interview at baseline (face-to-face) and three and twelve months later by telephone (both based on self-report). During the assessment by telephone, the research nurse reminded the patient of the VAS as it was assessed during the hospitalisation and asked whether they still remembered it. Before administering the VAS, they explained it to all the patients and in case of doubt, the explanation was repeated. In the course record form (CRF), there was space to make remarks about any irregularities. When checking these remarks, it was clear that some patients did not want to, or could not answer the VAS. If this was the case, their answer was left out.

The EQ-5D is the most widely used preference-based generic HRQOL instrument and it has well-established psychometric properties.[15] It has also been validated in patients with mild-moderate dementia.[16] The EQ-5D includes five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The respondent answers each of the EQ-5D's five dimensions with one of three possible responses: 'no problems', 'some problems' or 'severe problems'. The unique set of five responses defines a health state. The 243 (3^5) possible health states are weighted using a population-derived valuation from a sample of the Dutch general population known as the Dutch EQ-5D tariff. These values or utilities reflect the relative desirability of the health state and are measured on a scale where 1 refers to full health and 0 refers to death. Some health states are regarded as being worse than death, resulting in negative utilities with a minimum of -0.38.[17]

QALY is the product of a health state utility multiplied by the time the patient spent in this health state and then summed up to calculate the QALY.[18] An advantage of QALY is that the deceased participants could remain included in the analyses. For patients who died, we calculated QALY by using the retrieved dates of death and an utility score of 0 from that date on.

The VAS records the respondent's self-rated health on a scale from 0-100, where '100' refers to the best possible health state, and '0' to the worst. Respondents draw a line to the scale's point that best indicates their health state on that specific day.

Predictor variables

Predictor variables were factors previously found to be associated with decreased HRQOL, and variables that

we considered to be of clinical importance.[6-12,19] We divided these factors into three categories: 1) demographic characteristics, 2) comorbidity and 3) geriatric conditions.

Demographic characteristics

We extracted patients' age and sex at baseline from the medical records. During the interview, patients were asked about their living situation, ethnicity and education (in years).

Comorbidity

Comorbidity was retrieved from the discharge letter and systematically scored with the Charlson Comorbidity Index (CCI).[20] Scores range from 0 to 31, with higher scores indicating more and/or more severe comorbidity.

Geriatric conditions

Table 1 shows geriatric conditions as assessed during the systematic CGA, including internationally applied measurement instruments, score ranges and the cut-off scores used. Because a previous study suggested that the total number of geriatric conditions might have an impact on functional impairment,[21] we also created a variable 'number of geriatric conditions' by counting all geriatric conditions at baseline for individual patients.

Table 1. *Content of the comprehensive geriatric assessment*

Geriatric condition	Measurement instrument	Range of scores	Cut-off score
Somatic domain			
Number of medications	Counting the number of different medications	Continuous	≥5 indicates polypharmacy
Malnutrition	Short Nutritional Assessment Questionnaire (SNAQ)[35]	0-7	≥2 malnourished
Obesity	Body mass index = weight/length^2	13-64	> 30 indicates severe overweight
Pain	Visual analogue scale	0-10	≥ 4
Fall risk	Have you fallen two or more times in the past three months?	Yes or no	Yes
Presence of a pressure ulcer	Prevention and Pressure Ulcer Risk Score Evaluation (prePURSE)[36]	0-46	≥ 20
Indwelling urinary catheter	Presence of a catheter at admission	Yes or no	Yes
Constipation	Self-report of constipation at admission	Yes or no	Yes
Psychological domain			
Cognitive impairment	Mini-Mental State Examination (MMSE)[15]	0-30	≤ 24
Pre-existent cognitive impairment	Informant Questionnaire COgnitive DEcline – Short Form (IQCODE-SF)[37-38]	16 items, 1 – 5	≥ 63/80
Depressive symptoms	GDS-2, Geriatric Depression Scale-2[39]: two questions: 1. Have you felt sad, depressed or hopeless in the past month? 2. Have you lost interest in daily activities?	0-2	2
Delirium	Confusion Assessment Method[40]	0-4	Item 1 and 2, and item 3 and/or 4 are present
Functional domain			
Premorbid ADL and IADL functioning	Katz ADL index score and modified Katz ADL index score[41]	0-15	≥ 1
Vision impairment	Do you have problems with your vision, regardless of the use of glasses?	Yes or no	Yes
Hearing impairment	Do you have problems with hearing, regardless of the use of a hearing aid?	Yes or no	Yes
Mobility difficulty	Are you using a walking device?	Yes or no	Yes
Incontinence	Self-report of incontinence for urine or faeces at admission	Yes or no	Yes
Social domain			
High perceived burden of caregivers	Experienced burden of Informal Care (EDIZ)[42]	0-9	≥ 4

STATISTICAL ANALYSIS

Baseline characteristics

Demographic characteristics, comorbidity, prevalence and total of geriatric conditions and HRQOL scores were summarised using descriptive statistics. Ethnicity was dichotomised because there were few patients of non-Caucasian ethnicity (Surinamese, Moroccan or other). We compared patients who survived and those who died during the study using independent t-tests for continuous variables and chi-square tests for categorical and dichotomous variables.

EQ-5D domains

Domain-specific level of functioning according to the EQ-5D at baseline was summarised descriptively. We compared patient-reported problems in each domain of the EQ-5D between patients who survived and those who died during the study using chi-square tests.

Association of predictor variables with HRQOL at one year

The predictor variables were chosen prior to analyses. We pre-specified that if the correlation between two variables was more than 0.80, the least relevant one would be excluded to avoid collinearity. Univariate linear regression analysis and multivariable regression analysis (backward elimination approach) were used to determine the relationship between the baseline predictor variables and HRQOL outcomes at one year. We included variables with $p < 0.20$ from the univariate analysis, in the multivariable regression analyses and included utility at baseline as a covariate in all analyses. In the multivariable linear regression model, we set statistical significance at a two-sided p value of 0.20. The residuals versus predicted values were plotted to check the model fit. Sensitivity analyses were done with somatic diagnosis at admission and with specified comorbidity for all HRQOL outcomes (data available upon request). We performed all analyses using the Statistical Package for the Social Sciences (SPSS) version 19.0 (SPSS Inc, Chicago, IL).

RESULTS

Baseline characteristics

We included 473 patients in this HRQOL study. *Table 2* presents the baseline characteristics of the research population. Within one year, 146 patients had died (30%). Among the deceased patients there were more men compared with those who survived (54.1 vs. 41.3%, $p = 0.01$). Compared with survivors, the deceased patients demonstrated a higher frequency of malnutrition (63.3 vs. 40.8%, $p < 0.001$), delirium (13.1 vs. 6.2%, $p = 0.01$), a higher mean CCI (5.1 vs. 3.2, $p < 0.001$) and a higher number of geriatric conditions at baseline (6.1 ± 2.5 vs. 5.1 ± 2.4, $p < 0.001$). Among the deceased, more patients had diagnosed malignancies (18.6 vs. 4.6%) and less had infectious diseases (26.4 vs. 42.3%), $p < 0.001$. Baseline mean utility (0.701 vs. 0.575) and VAS scores (56.5 vs. 63.0) were significantly lower for deceased compared with survivors ($p < 0.001$).

EQ-5D domains

Figure 1 shows the EQ-5D domains at baseline. Participants who survived were more likely to score 'no problems' and less likely to score 'moderate' or 'severe problems' in all domains, except for the domain 'anxiety/depression', where survivors more often scored 'severe problems'.

Association of predictor variables with HRQOL at 12 months

No collinearity between predictor variables was detected, with all correlations being well below 0.80 (range 0.15 to 0.67). *Table 3* shows the results of the univariable regression models. Variables printed in bold were included in the multivariable analyses. In the multivariable analyses (*table 4*), Caucasian ethnicity, higher malnutrition score, higher CCI and number of geriatric conditions were associated with lower one-year utility. Obesity and higher baseline utility were associated with higher one-year utility. The final model explained 33.4% of the variance.

For QALY, higher malnutrition score, higher delirium and depression scores, impaired hearing and worse premorbid functioning were associated with lower QALY. Higher baseline utility was associated with higher QALY. This final model accounted for 42.4% of the variance.

More medication, impaired hearing, higher CCI and lower VAS score at baseline were significantly associated with a lower VAS score at one-year follow-up. For the VAS score at one year, explained variance was 15.9%.

Sensitivity analyses showed similar results. From these analyses it became clear that CCI was a good measure for comorbidity. Introducing individual comorbid diseases did not change the models, nor did the different reasons for admission. The residuals versus predicted values plotted for utility and VAS at one year and QALY looked normal.

DISCUSSION

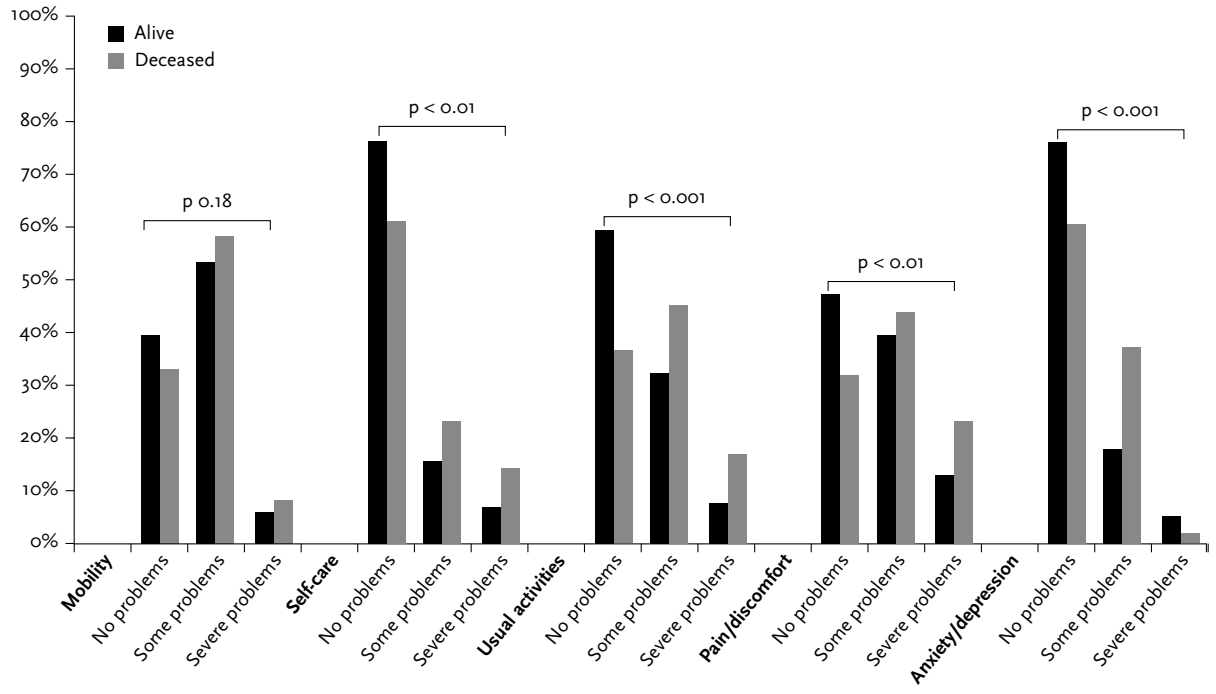
This multicentre prospective cohort study demonstrates that, in acutely admitted older patients, utility and VAS score at baseline were significantly higher for patients who survived than for patients who died during one year of follow-up. Higher baseline utility, reflecting better HRQOL, was associated with higher one-year utility and QALY. Higher CCI, malnutrition and pressure ulcers were associated with lower HRQOL outcomes at one year. A higher number of geriatric conditions at baseline was

Table 2. *Baseline description of acutely admitted older patients with utility score at baseline (n = 473)*

Variable	Missing values n (%)	All participants n = 473	Surviving participants n = 327	Deceased participants n = 146	P*
Demographic					
Age, mean (SD)	0 (0.0)	77.8 (7.6)	77.7 (7.4)	78.1 (7.9)	0.60
Female sex	0 (0.0)	54.8	58.7	45.9	0.01
Ethnicity: Caucasian	1 (0.2)	94.1	92.6	97.9	0.02
Social status: single	1 (0.2)	48.5	50.9	43.2	0.14
Living situation: independent	1 (0.2)	88.3	89.3	86.3	0.36
Years of education, mean (SD)	7 (1.5)	10.1 (4.0)	10.2 (4.0)	10.1 (3.8)	0.79
Somatic domain					
No. medications, mean (SD)	2 (0.4)	5.9 (4.2)	5.8 (4.2)	6.0 (4.0)	0.52
Malnutrition†	1 (0.2)	47.7	40.8	63.3	< 0.001
Obesity‡	40 (8.5)	13.6	17.4	5.2	< 0.001
Pain§	1 (0.2)	43.0	43.4	42.1	0.78
Fall risk, ≥ 2 falls in last 3 months	23 (4.7)	19.8	17.7	24.5	0.10
Presence of a pressure ulcer‖	7 (1.5)	13.7	13.0	15.4	0.49
Indwelling urinary catheter	3 (0.6)	19.8	18.4	22.9	0.26
Constipation	4 (0.8)	18.8	17.3	22.1	0.25
Psychological domain					
Cognitive impairment at admission¶	0 (0.0)	30.2	29.4	32.2	0.54
Depressive symptoms**	2 (0.4)	21.2	18.7	26.9	0.05
Delirium††	5 (1.1)	8.3	6.2	13.1	0.01
Functional domain					
Functional impairment‡‡	0 (0.0)	85.4	83.8	89.0	0.14
Impaired vision	15 (3.2)	20.3	20.7	19.6	0.80
Impaired hearing	34 (7.2)	18.0	16.2	22.1	0.14
Use of walking device	0	56.2	52.9	63.7	0.04
Incontinence	17 (3.6)	19.5	19.0	20.6	0.70
Social domain					
High burden informal care giver§§	75 (15.6)	38.2	33.7	48.0	0.01
Diagnosis at admission, n (%)	26 (5.5)				< 0.001
Cardiovascular disease		8.9	8.1	10.7	
Disease of the digestive system		22.6	23.1	21.4	
Infectious disease		37.4	42.3	26.4	
Malignancy		8.9	4.6	18.6	
Water and electrolyte disturbance		7.2	7.5	6.4	
Other diagnosis at admission		15.0	14.3	16.4	
Comorbidity index‖‖, mean (SD)	45 (9.5)	3.8 (2.5)	3.2 (2.1)	5.1 (2.7)	< 0.001
Number of geriatric conditions¶¶, mean (SD)	0 (0.0)	5.4 (2.5)	5.1 (2.4)	6.1 (2.5)	< 0.001
Utility at baseline, mean (SD)	0 (0.0)		0.70 (0.29)	0.58 (0.32)	< 0.001
VAS at baseline, mean (SD)	8 (1.7)	61.0 (18.4)	63.0 (18.5)	56.5 (17.6)	< 0.001

Values are percentages unless stated otherwise.
*p: independent t-test for continuous variables, chi-square for categorical variables. †Short Nutritional Assessment Questionnaire (SNAQ), score 2-7; ‡Body Mass Index (BMI)= weight/length^2 ≥ 30; §Visual analogue scale for pain, score ≥ 4; ‖Prevention and Pressure Ulcer Risk Score Evaluation (prePURSE), score ≥ 20; ¶Mini Mental State Examination (MMSE), ≤ 24; **Geriatric Depression Scale-2, 2 questions, depressive symptoms present when both positive; ††Confusion Assessment Method, score 3 or 4; ‡‡ (modified) KATZ-ADL index, score ≥ 1; §§Experienced Burden of Informal Care (EDIZ), score ≥ 4; ‖‖Charlson comorbidity index score, higher score indicates more and/or more severe comorbidity; ¶¶Total number of geriatric conditions, 0-18, a higher score indicates more geriatric conditions present.

Figure 1. *EQ5D domain-specific responses at baseline for patients who survived (n = 327) and for patients who died during the study (n = 146)*



Panel shows percentages of patient-reported severity of problems at EQ-5D domains at baseline. Black bars represent the 327 patients who survived during the study; grey bars represent the 146 patients who died within one year.

associated with lower one-year utility, and this association was stronger than for any individual geriatric condition. More depressive symptoms, higher delirium score and worse premorbid functioning were associated with worse QALY. Our results suggest that besides the acute illness and comorbidity, geriatric conditions highly influence HRQOL one year after admission, and that they should be assessed at hospital admission.

In our study, baseline EQ-5D domain scores, mean utility and VAS scores were lower than in European and Dutch norm-population studies.[6,22] This confirms that our research population forms a very vulnerable patient group, which is also reflected by the high number of geriatric conditions at baseline and by the high mortality rate after one year. At baseline, deceased patients had a higher number of geriatric conditions, higher CCI and worse scores on most individual EQ-5D domains than patients who survived. This is in agreement with previous studies evaluating older patients.[23-25] A hypothesis for the fact that surviving patients more often scored 'severe problems' on the 'anxiety/depression' domain at baseline, might be that their better cognitive function at admission (as measured by MMSE), may have resulted in more awareness of their situation, and thus anxiety.

To our knowledge, the association between a higher number of geriatric conditions at baseline and lower one-year HRQOL expressed in utility has not been demonstrated before in acutely hospitalised patients, although prior research confirmed the influence of individual geriatric conditions on mortality,[3] and thus indirectly on QALY. Some demographic variables, which were previously shown to be associated with HRQOL, were not associated with HRQOL in our multivariable analyses. This might be due to the many geriatric conditions and the high comorbidity rate in our population, which may overrule the effects of these variables. Patients who were obese were more likely to survive and they had higher utility scores at one year than patients who were not obese. This may be an example of the obesity paradox, which describes the unexpected phenomenon that in some cases overweight and obese patients have better outcomes and less mortality compared with their normal-weight counterparts. For patients older than 70 years, a protective effect of overweight and obesity has been observed before.[26-28]

Explained variance of the final models for utility and QALY were good. This means that the geriatric conditions, CCI and lower utility at baseline explained 33.4 and 42.4%,

Table 3. *Univariable analyses for utility, VAS score and QALY at one year*

	Utility at one year (n = 423)			VAS score at one year (n = 260)			QALY at one year (n = 380)		
Variables	**B**	**95% CI**	**P**	**B**	**95% CI**	**P**	**B**	**95% CI**	**P**
Demographic									
Age	0.00	-0.01 – 0.00	0.48	-0.05	-0.30 – 0.19	0.67	-0.00	-0.01 -0.00	**0.08**
Male sex	0.11	0.05 – 0.18	**< 0.01**	1.68	-1.97 – 5.33	0.37	-0.02	-0.09 – 0.06	0.64
Caucasian ethnicity	-0.10	-0.24 – 0.03	**0.13**	1.68	-5.53 – 8.89	0.65	0.04	-0.03 – 0.12	0.23
Social status: single	0.08	0.02 – 0.15	**0.01**	-1.57	-5.13 – 2.00	0.39	-0.01	-0.07 – 0.06	0.87
Living independently	0.16	0.05 – 0.28	**0.01**	6.22	0.22 – 12.22	**0.04**	-0.05	-0.09 – -0.01	**0.01**
Education, years	0.01	0.00 – 0.01	**0.26**	0.03	-0.42 – 0.47	0.91	0.01	0.00 – 0.02	**0.10**
Somatic domain									
No. medications	-0.02	-0.03 – -0.01	**< 0.01**	-0.80	-1.40 – -0.20	**0.01**	-0.01	-0.02 – 0.00	**0.10**
Malnutrition score†	-0.02	-0.03 – 0.00	**0.06**	-0.89	-1.78 – 0.01	**0.05**	-0.05	-0.06 – -0.03	**< 0.001**
Obesity‡	-0.09	-0.18 – -0.01	**0.04**	-2.43	-7.12 – 2.26	0.31	-0.06	-0.18 – 0.06	0.30
Pain score§	-0.03	-0.04 – -0.02	**< 0.001**	-0.83	-1.46 – 0.19	**0.01**	-0.02	-0.04 – -0.01	**< 0.01**
Fall risk	-0.08	-0.17 – 0.02	**0.11**	-4.63	-9.36 – 0.38	**0.07**	-0.14	-0.23 – -0.04	**< 0.01**
Pressure ulcer score‖	-0.01	-0.02 – 0.00	**0.01**	-0.26	-0.59 – 0.07	**0.12**	-0.01	-0.02 – -0.01	**< 0.001**
Indwelling urinary catheter	-0.07	-0.17 – 0.03	**0.15**	-2.22	-7.02 – 2.58	0.36	-0.04	-0.12 – 0.04	0.36
Constipation	-0.07	-0.16 – 0.02	**0.10**	-0.84	-5.59 – 3.90	0.73	-0.08	-0.17 – 0.01	**0.09**
Psychological domain									
MMSE score¶	0.01	0.00 – 0.02	**0.05**	-0.17	-0.70 – 0.37	0.55	0.02	0.01 – 0.03	**< 0.001**
Depressive symptoms**	-0.09	-0.13 – -0.05	**< 0.001**	-3.45	-5.77 – -1.12	**<0.01**	-0.11	-0.15 – -0.06	**< 0.001**
Delirium, CAM score††	-0.03	-0.08 – 0.01	**0.18**	0.82	-1.59 – 3.29	0.50	-0.08	-0.13 – -0.03	**< 0.01**
Functional domain									
Premorbid functioning‡‡	-0.03	-0.04 – -0.02	**< 0.001**	-0.79	-1.33 – -0.25	**<0.01**	-0.04	-0.05 – -0.03	**< 0.001**
Impaired vision	-0.11	-0.19 – -0.03	**0.01**	-3.73	-8.04 – 0.58	**0.09**	-0.06	-0.14 – 0.03	0.22
Impaired hearing	-0.02	-0.11 – 0.08	0.69	-0.35	-8.58 – 1.53	**0.17**	-0.10	-0.19 – 0.00	**0.05**
Use of walking device	-0.08	-0.11 – -0.05	**< 0.001**	-2.04	-3.80 – -0.27	**0.02**	-0.07	-0.10 – -0.05	**< 0.001**
Incontinence	-0.07	-0.16 – 0.02	**0.11**	-1.62	-3.19 – 6.44	0.51	-0.08	-0.18 – 0.01	**0.08**
Social domain									
Burden care giver§§	-0.02	-0.03 – -0.01	**< 0.01**	-0.77	-1.43 – -1.12	**0.02**	-0.04	-0.05 – -0.02	**< 0.001**
Comorbidity index‖‖	-0.06	-0.07 – -0.04	**< 0.001**	-1.05	-1.99 – -0.12	**0.03**	-0.05	-0.06 – -0.03	**< 0.001**
No. geriatric conditions¶¶	-0.05	-0.07 – -0.04	**< 0.001**	-1.74	-2.24 – -1.03	**<0.001**	-0.06	-0.08 – -0.05	**< 0.001**
Utility baseline	0.39	0.28 – 0.50	**< 0.001**	10.81	4.76 – 16.95	**<0.01**	0.55	0.44 – 0.65	**< 0.001**
VAS baseline	0.00	0.00 – 0.01	**< 0.001**	0.24	0.14 – 0.34	**<0.001**	0.01	0.00 – 0.01	**< 0.001**

CI = confidence interval; †Short Nutritional Assessment Questionnaire (SNAQ), score 2-7; ‡Body Mass Index (BMI)= weight/length² ≥ 30; §Visual analogue scale for pain, score ≥ 4; ‖Prevention and Pressure Ulcer Risk Score Evaluation (prePURSE), score ≥ 20; ¶Mini Mental State Examination (MMSE), ≤ 24; **Geriatric Depression Scale-2, 2 questions, depressive symptoms present when both positive; ††Confusion Assessment Method, score 3 or 4; ‡‡(modified) KATZ-ADL index, score ≥ 1; §§Experienced Burden of Informal Care (EDIZ), score ≥ 4; ‖‖Charlson comorbidity index score, higher score indicates more and/or more severe comorbidity; ¶¶Total number of geriatric conditions, 0-18, a higher score indicates more geriatric conditions present.

Table 4. *Multivariable analyses for utility, VAS score and QALY at one year*

	Utility at one year (n = 423)			VAS score at one year (n = 260)			QALY at one year (n = 380)		
Variables	**B**	**95% CI**	**P < 0.20**	**B**	**95% CI**	**P < 0.20**	**B**	**95% CI**	**P < 0.20**
Demographic									
Age	-	-	-				-	-	-
Male sex	-	-	-						
Caucasian ethnicity	-0.24	-0.40 – -0.08	< 0.01						
Social status: single	-	-	-						
Living independently	-	-	-	-	-	-	-	-	-
Education, years.							-	-	-
Somatic domain									
No. medications	-	-	-	-0.59	-1.06 – -0.11	0.02	-	-	-
Malnutrition score†	-0.02	-0.04 – 0.00	0.08	-	-	-	-0.02	-0.04 – -0.01	0.01
Obesity‡	0.11	0.01 – 0.22	0.04						
Pain score§	-	-	-	-	-	-	-0.01	-0.02 – 0.00	0.05
Fall risk	-	-	-	-	-	-	-	-	-
Pressure ulcer score‖	-0.01	-0.02 – 0.00	0.05	-	-	-	-0.01	-0.02 – 0.00	0.01
Indwelling urinary catheter	0.09	-0.01 – 0.20	0.08						
Constipation	-	-	-				-	-	-
Psychological domain									
MMSE score¶	-	-	-				-	-	-
Depressive symptoms**	-	-	-	-	-	-	-0.03	-0.07 – 0.01	0.20
Delirium, CAM score††	-	-	-				-0.05	-0.10 – -0.01	0.02
Functional domain									
Premorbid functioning‡‡	-	-	-	-	-	-	-0.02	-0.03 – -0.01	< 0.01
Impaired vision				-	-	-			
Impaired hearing	-	-	-	-3.51	-8.68 – 1.66	0.18	-0.09	-0.17 – -0.01	0.03
Use of walking device	-	-	-	-	-	-	-	-	-
Incontinence	-	-	-				-	-	-
Social domain									
Burden care giver§§	-	-	-	-	-	-	-	-	-
Comorbidity index‖‖	-0.05	-0.06 – -0.03	< 0.001	-1.03	-2.06 – 0.00	0.05	-0.04	-0.05 – -0.03	< 0.001
No. geriatric conditions¶¶	-0.03	-0.05 – -0.01	< 0.01	-	-	-	-	-	-
Utility baseline	0.25	0.11 – 0.39	< 0.01	3.58	-3.70 – 10.86	0.33	0.31	0.17 – 0.45	< 0.001
VAS baseline				0.19	0.08 – 0.30	< 0.01	-	-	-
Variance explained R2	33.4%	15.9%	42.4%						

CI = confidence interval; †Short Nutritional Assessment Questionnaire (SNAQ), score 2-7; ‡Body Mass Index (BMI)= weight/length² ≥30; §Visual analogue scale for pain, score ≥4; ‖Prevention and Pressure Ulcer Risk Score Evaluation (prePURSE), score ≥20; ¶Mini Mental State Examination (MMSE), ≤ 24; **Geriatric Depression Scale-2, 2 questions, depressive symptoms present when both positive; ††Confusion Assessment Method, score 3 or 4; ‡‡(modified) KATZ-ADL index, score ≥1; §§Experienced Burden of Informal Care (EDIZ), score ≥4; ‖‖Charlson comorbidity index score, higher score indicates more and/or more severe comorbidity; ¶¶Total number of geriatric conditions, 0-18, a higher score indicates more geriatric conditions present.

respectively, of the variance and contributed to lower HRQOL. Because many of the geriatric conditions assessed in our study can be adequately treated during and after admission, it is of clinical importance to assess the geriatric conditions and other predictor variables included in our models upon acute admission of a patient of 65 years and older. A systematic approach in detecting these geriatric conditions by means of a CGA might significantly improve the patient's HRQOL. For the VAS score, the explained variance was lower. This might be because it is the patient's own reflection on her or his HRQOL, which is mainly influenced by individual coping style and adaptation, and not so much by the objective CGA variables.[29]

There are some limitations to our study. First, patients with an MMSE score below 16 were excluded, because their HRQOL could not be measured reliably with the EQ-5D.[14-16,30] Because they had a significantly higher number of geriatric conditions at baseline in comparison with patients with an MMSE score above 16, we expect their HRQOL would have been even lower.[31] Several instruments are available for measuring HRQOL in dementia patients, but none is validated for severely demented patients.[32,33] Secondly, we administered the EQ-5D by telephone during follow-up. The lack of a visual representation of the VAS might have resulted in participants scoring whole numbers, or numbers that could be divided by five, instead of using a continuous count (e.g. 80 or 85, instead of 83), but no evidence of this could be found in the literature. However, the nature of EQ-5D instructions in the face-to-face and telephone administration is similar, and McPhail *et al.*, found that telephone administration of EQ-5D provided comparable results to face-to-face administration amongst older adults who seemed to have intact cognitive functioning at baseline.[34] Thirdly, we did not ask our patients' opinion regarding the relevance of their HRQOL, which might provide an even better understanding of HRQOL in acutely admitted older patients. Therefore, future research could study minimal clinically important changes in HRQOL and the effect of baseline HRQOL on outcome in terms of functionality and survival, possibly enabling advice to be further tailored to the individual.

In conclusion, for acutely admitted older patients, less comorbidity and geriatric conditions and better baseline HRQOL are associated with better HRQOL one year after admission. In this vulnerable, but very common patient group, comorbidity can generally not be modified by medical treatments, so it is of utmost importance to try and concentrate on factors that can be improved, such as delirium, malnutrition, pressure ulcers and hearing impairment. Baseline evaluation of these factors at admission by means of a CGA could guide patient, family, and professionals in determining goals to achieve during admission with the ultimate goal of improving HRQOL after discharge.

PREVIOUS PRESENTATION

Oral presentation at the 9th International Congress of the European Union Geriatric Medicine Society (EUGMS), in Venice, Italy, 2-4 October 2013. http://www.eugms2013.it/

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DISCLOSURES

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CASE REPORT

An African woman with pulmonary cavities: TB or not TB?

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ABSTRACT

Cavitary lung lesions in patients from developing countries are mostly caused by tuberculosis (TB). However, when TB cannot be confirmed, a primary lung abscess caused by anaerobic bacteria from the mouth should be considered, especially in patients with poor dentition. We present a case of a Sudanese woman with a cavitary lung lesion and severe gingivitis. *Bulleidia extructa* was isolated as a single pathogen from the pulmonary cavity.

KEYWORDS

Anaerobic bacteria, lung abscess, periodontitis

What was known on this topic?
A pulmonary cavity is a gas-filled area of the lung in the centre of a nodule or area of consolidation. It may be detected by plain chest radiography or computed tomography. Cavitary lung lesions are frequent manifestations of a wide variety of infectious and non-infectious processes involving the lung. In patients originating from TB-endemic countries, TB is the most likely cause.

What does this add?
We show, for the first time, that the anaerobic rod *Bulleidia extructa* was isolated as the causative agent in a primary lung abscess. Clinicians should be aware that a cavitary lung lesion in a patient from a TB-endemic country is not always caused by TB. Poor dentition should raise suspicion of a lung abscess caused by oral anaerobic bacteria. The treatment duration should be long enough.

INTRODUCTION

Cavitary lung lesions can be caused by a broad range of necrotising infections and non-infectious diseases. In immigrants from Third World countries tuberculosis (TB) is the most likely cause. If TB cannot be confirmed, other causes should be considered. We present a case of a Sudanese woman with multiple pulmonary cavities negative for *Mycobacterium tuberculosis*. *Bulleidia extructa*, an anaerobic rod found in gingivitis was isolated as the causative agent in a primary lung abscess.

CASE REPORT

A 56-year-old HIV-negative Sudanese woman presented with a persistent productive cough and fever, four years after coming to the Netherlands. Elsewhere, chest radiography and computed tomography (CT) showed an infiltrate with a cavitary lesion in the left upper lobe. Bronchoscopy was normal, the tuberculin skin test was negative and repeated examinations of sputum and bronchoalveolar lavage were negative for *Mycobacterium tuberculosis* (microscopy, culture, and PCR). CT-guided transthoracic aspirate showed chronic, non-specific inflammation and again, the cultures were

negative. Amoxicillin-clavulanic acid for ten days led to a temporary improvement of the symptoms. Three months later she returned with fever, cough, and haemoptysis. The CT scan showed progression of the cavitary lesion (*figure 1*). Even though sputum cultures were negative, ciprofloxacin was given for ten days. She did not improve and was referred to our hospital where she reported progressive cough, haemoptysis and weight loss. She reported a tooth extraction two months before the start of her symptoms. In the last six months, her daughter had noticed an extremely putrid smell on her mother's breath. On physical examination she was febrile (38.5 °C) with very poor dentition, periodontitis, and a prominent fetor ex ore. Laboratory investigations showed anaemia and mild leukocytosis. Chest radiography and CT scan showed extensive consolidations in the left upper lobe, with multiple cavities filled with fluid and air. Orthopantomography showed extensive general periodontitis with periapical radiolucencies of multiple teeth (*figure 2*).

Bronchoscopy showed massive secretion from the left upper lobe, with large amounts of a single species of gram-positive anaerobic rods cultured. Using 16S PCR analysis this was identified as *Bulleidia extructa*, a pathogen until now only described in periodontitis, and recently in a total hip arthroplasty infection.[1-3] The patient underwent extraction of the diseased teeth and was treated with 600 mg clindamycin orally three times a day for two months, after which she showed complete clinical and radiological recovery.

Figure 1. *Computed tomography scan showing progression of the cavitary lesion*

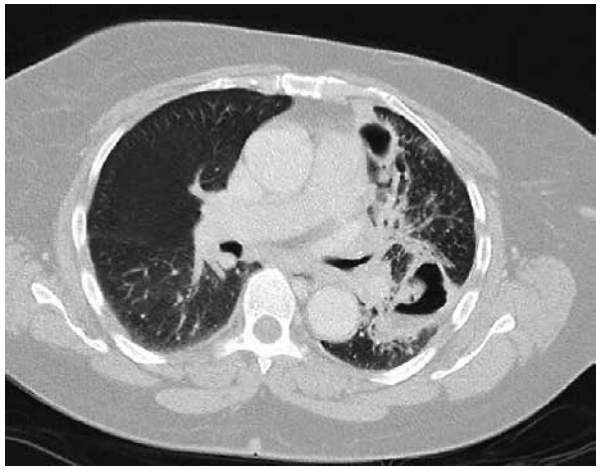
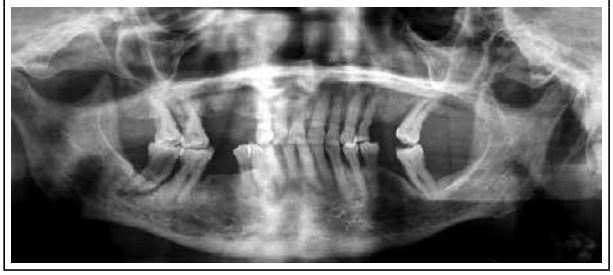


Figure 2. *Orthopantomogram showing extensive general periodontitis with periapical radiolucencies of multiple teeth*



DISCUSSION

Primary lung abscesses are usually caused by aspiration of anaerobic bacteria present in the gingival crevices and dental pockets,[4] sometimes associated with altered consciousness (e.g. alcoholism), dysphagia, oesophageal disease or recent tooth extractions. Patients commonly have poor dentition with periodontitis, resulting in an unusually high load of oral anaerobic organisms. Lung abscesses are rare in edentulous patients, in which case airway obstruction (e.g. bronchogenic carcinoma) should be suspected. Aspiration most frequently occurs in the supine patient and therefore lung abscesses mostly occur in the posterior segment of the right and left upper lobe.

Patients generally present with slowly progressive symptoms of fever, productive cough, malaise and weight loss, and sometimes haemoptysis. Rigors are rare. Many patients and their close contacts complain of a putrid smell on the patient's breath. Physical examination frequently shows gingival crevice disease with dental pockets and other signs of periodontitis; lung auscultation may be abnormal. Anaemia of chronic disease and leucocytosis are usually present. Chest radiography typically shows a cavitary lesion with an air-fluid level, and computed tomography should exclude an associated obstructing endobronchial lesion.

The most frequently isolated anaerobes are *Peptostreptococcus* spp., *Fusobacterium nucleatum* and *Prevotella melaninogenica*.[5] Cultures usually show multiple anaerobic species, and microaerophilic streptococci and *S. milleri* in mixed infections. In a typical case, therapy may be initiated without microbiological diagnosis. Isolation of the causative pathogens is difficult since sputum or bronchoscopy aspirates are often contaminated by upper airway flora.

Historically penicillin was the treatment of choice for anaerobic lung abscess, but clindamycin is the preferred drug today. More anaerobes including *Prevotella* spp, *Bacteroides* spp (non fragilis) and *Fusobacteria* now produce penicillinase, and two trials demonstrated superiority of clindamycin compared with parenteral penicillin.[6,7] Metronidazole often leads to failure due to the presence of aerobic and microaerophilic streptococci in mixed infections.

No studies have evaluated optimum duration of treatment. Our patient was initially treated with amoxicillin-clavulanic acid for ten days, but patients should probably be treated for 6-8 weeks or more, until chest radiography has markedly improved or even normalised. Surgery is rarely indicated and bronchoscopic drainage should be reserved for patients with an obstructing lesion. Of course, the origin of the lung infection needs causative treatment, in this case complete extraction of the diseased dentition.
In conclusion, cavitary lung lesions in a patient from a TB-endemic country are not always caused by TB. Poor dentition should raise suspicion of a lung abscess caused by oral anaerobic bacteria; the treatment duration should be long enough.

DISCLOSURES

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

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Netherlands
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PHOTO QUIZ

A rare cause of haematuria

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CASE REPORT

A 36-year-old man with an unremarkable medical history presented to our emergency department with continuous lower abdominal pain radiating to the right side with fulminant macroscopic haematuria that started two hours earlier. Two weeks before admission the patient was treated with amoxicillin by the general practitioner for suspected pyelonephritis. Three days prior to admission the patient started using diclofenac because of increasing right-sided lumbar pain. There was no history of fever, chills, haematuria, pyuria or trauma. There was no positive family history of renal diseases. Physical examination revealed signs of shock (regular pulse 135 beats/minute; blood pressure 125/75 mmHg at presentation decreasing to 94/55 mmHg after one hour), with severe tenderness at the right costovertebral angle. Routine laboratory investigations showed anaemia (haemoglobin 5.5 mmol/l), serum creatinine 193 µmol/l, hyperkalaemia 5.3 mmol/l, lactate 5.2 mmol/l and a marked leucocytosis $36.2*10^9$/l. The fibrinogen, prothrombin time, partial thromboplastin time and thrombocyte count were all normal. The symptoms suggested intra-abdominal bleeding with compression of the ureteral structures. A contrast-enhanced computed tomography (CT) of the abdomen and pelvis was performed.

WHAT IS YOUR DIAGNOSIS?

See page 433 for the answer to this photo quiz.

Netherlands
The Journal of Medicine

PHOTO QUIZ

A young man with intermittent abdominal pain and anaemia: a peculiar finding

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CASE REPORT

A 23-year-old Asian man presented with a one-year history of intermittent cramping abdominal pain, followed by nausea and vomiting. At presentation, symptoms occurred two to three times a day and lasted for a few minutes to half an hour. Neither constipation nor diarrhoea or bloody stools were present and his weight was stable. Past medical history revealed a recent diagnosis of iron-deficiency anaemia for which he received iron supplements.

On physical examination the abdomen was soft with normal bowel sounds and no tenderness. Laboratory investigations showed microcytic anaemia (haemoglobin 7.7 g/dl) and no other abnormalities. Previous upper and lower endoscopy were unremarkable, with the exception of a mild non-specific gastritis for which he had been taking a proton-pomp inhibitor for two months.

Figure 1. *Abdominal CT, thickened small bowel wall within a proximal jejunum loop*

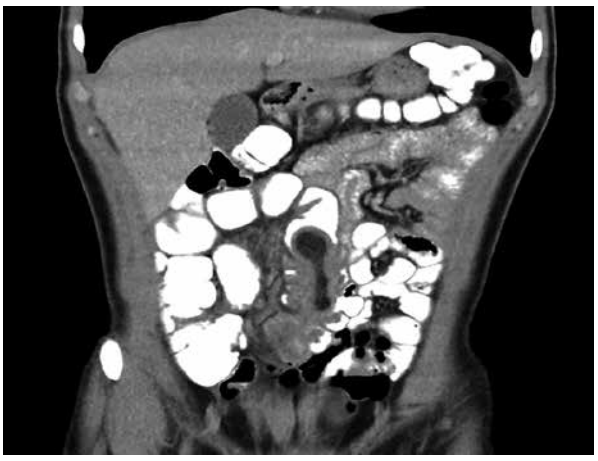
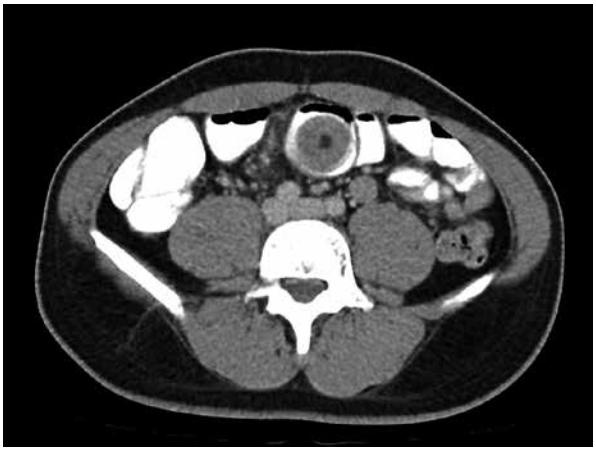


Figure 2. *Abdominal CT, axial plane, target-shape lesion*



Abdominal computed tomography demonstrated a thickened small bowel wall within a proximal jejunum loop (*figure 1*) as a target-shape lesion in the axial plane (*figure 2*).

WHAT IS YOUR DIAGNOSIS?

See page 434 for the answer to this photo quiz.

Netherlands
The Journal of Medicine

PHOTO QUIZ

A lung cancer patient with painful fingers

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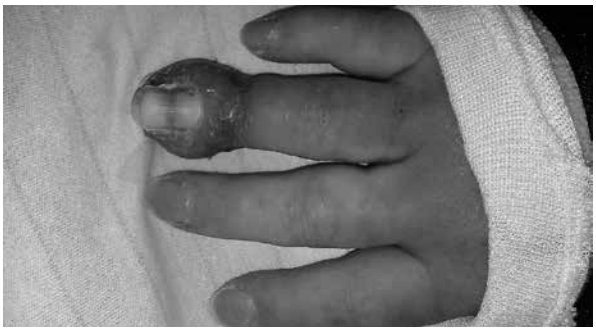
CASE REPORT

A 59-year-old man with a recently diagnosed T4N2M1 squamous cell carcinoma of the lung with hepatic and adrenal gland metastasis presented after the third chemotherapy cycle with a painful fourth finger of the right hand. Physical examination revealed swelling, redness and tenderness of the distal phalanx of the fourth digit of the right hand (*figure 1*).

Under suspicion of a panaritium, the patient was referred to a surgeon for incision and drainage, but exploration did not reveal any pus. The differential diagnosis included arthritis for which he was treated with prednisone. However, after two weeks of prednisone treatment, there was no improvement. Now he also had symptoms of the left hand. Additional X-rays of the hands were performed (*figure 2 and 3*).

Figure 1. *Swelling, redness and tenderness of the distal phalanx of the fourth digit of the right hand at initial presentation*



WHAT IS YOUR DIAGNOSIS?

See page 435 for the answer to this photo quiz.

Figure 2. *Anteroposterior radiographs of the right hand; complete destruction of the bone of the distal phalanx of the fourth digit of the right hand*

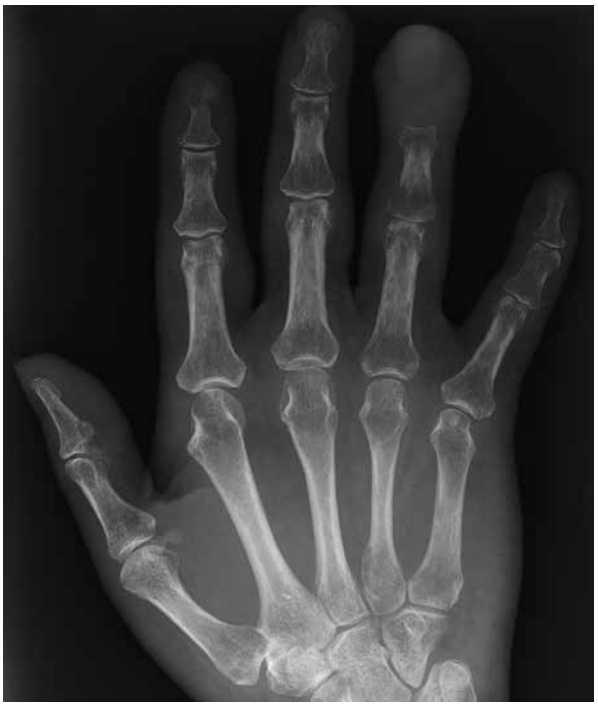
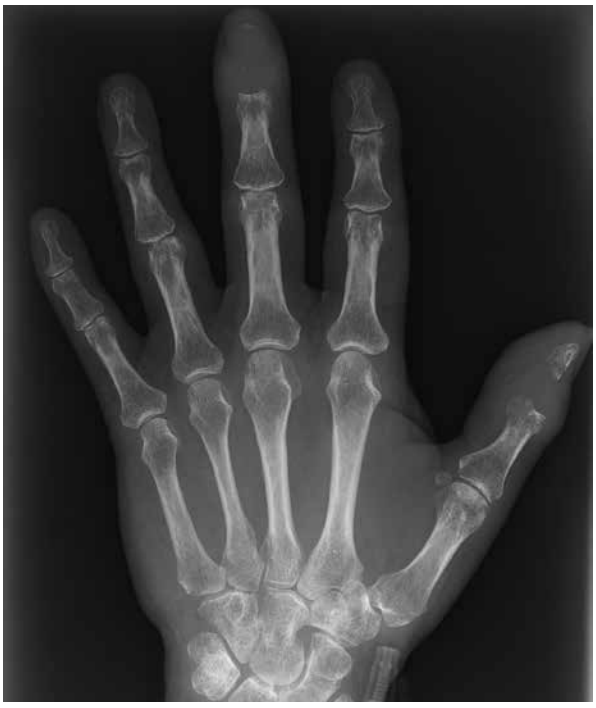


Figure 3. *Anteroposterior radiographs of the left hand: substantial osteolysis of the distal phalanx of the first and third digit of the left hand*



Netherlands
The Journal of Medicine

PHOTO QUIZ

A 41-year-old man with an increased abdominal girth

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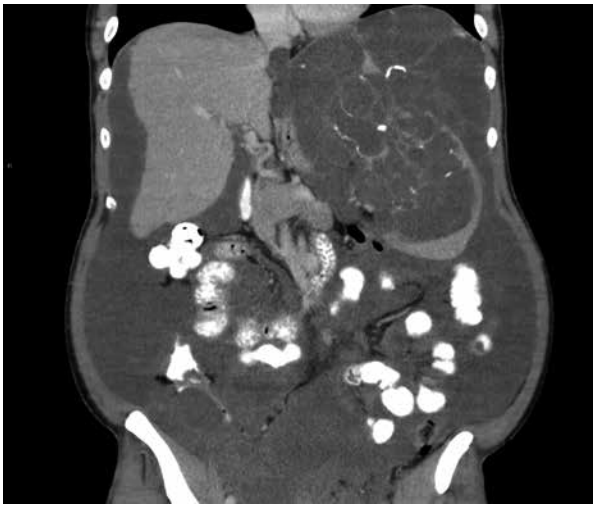
*corresponding author: e-mail: lindabecude@gmail.com

CASE REPORT

A 41-year-old man with no notable medical history was referred to the internal medicine ward because of an increasing abdominal girth and a weight loss of 21 kg. He denied stomach ache, a change in bowel movements, anorexia or night sweats. Physical examination revealed an abdominal distension with a protruded umbilicus and diffuse hyporesonant percussion without evident shifting dullness. A contrast-enhanced computed tomography (CT) scan was performed.

Figure 1. *A contrast-enhanced computed tomography of the abdomen*



WHAT IS YOUR DIAGNOSIS?

See page 436 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 429)

A RARE CAUSE OF HAEMATURIA

DIAGNOSIS

Wunderlich's syndrome as a first manifestation of a renal angiomyolipoma

CT of the abdomen revealed massive (*figure 1, arrow*) active bleeding (*figure 2, arrow*) in the region of the right kidney. The kidney was enlarged, deformed and anteriorly displaced due to the haematoma with secondary upward displacement of the liver. The kidney showed a mass of approximately 9 x 9 x 9 cm with irregular contrast enhancement and focal black areas of fat as measured by their density.

The mass was likely to be an angiomyolipoma. A selective arterial embolisation of a side branch of the right renal artery was performed and stopped the renal bleeding. Recovery was uneventful and renal function normalised.

Severe acute subcapsular or perirenal bleeding was first clinically described by Carl August Wunderlich.[1] Wunderlich's syndrome is classically defined as non-traumatic spontaneous renal bleeding that can be caused by tumours, inflammatory vascular diseases, cysts, renal artery aneurysms, a renal vein thrombosis or arteriovenous malformations. However, the major cause of Wunderlich's syndrome is a renal angiomyolipoma.[2] Angiomyolipomas are rare, benign fat and myocyte-containing tumours often with a vulnerable vasculature found at approximately 0.3 to 2.1% of routine autopsies.[3] The chance of spontaneous rupture and bleeding increases in proportion to the size of the tumour and the degree of neovascularisation.[4] In general, close echographic follow-up or even prophylactic embolisation is advised in patients with an asymptomatic angiomyolipoma larger than 4 cm. The most common therapy for Wunderlich's syndrome is selective arterial embolisation, which often preserves the renal function. Unlike this case, these tumours are associated with tuberous sclerosis, which is present in approximately 10% of cases. Patients should be examined for characteristic skin lesions and other benign tumours (e.g. pulmonary lymphangioleiomyomatosis). Differentiation with renal epitheloid angiomyolipoma should be made as these tumours are associated with malignant degeneration. However, if intrarenal fat is found on CT, this rules out epitheloid angiomyolipoma.[5]

Figure 1. *Transverse CT scan of the abdomen*

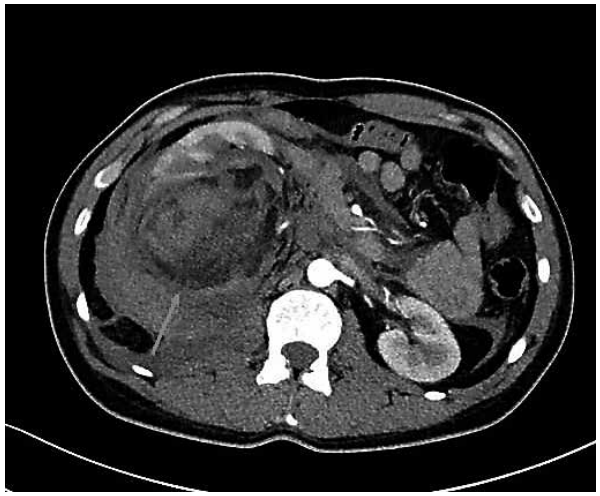
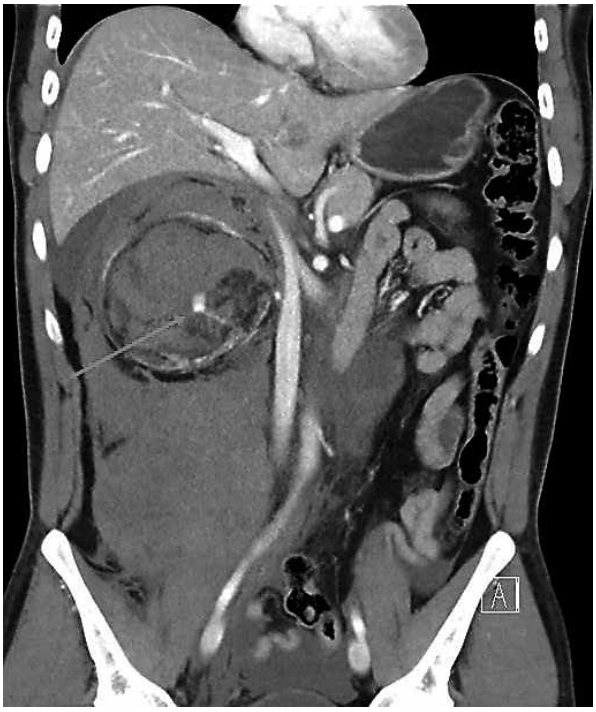


Figure 2. *Coronal CT scan of the abdomen*



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ANSWER TO PHOTO QUIZ (PAGE 430)

A YOUNG MAN WITH INTERMITTENT ABDOMINAL PAIN AND ANAEMIA: A PECULIAR FINDING

DIAGNOSIS

Clinical history and radiological findings suggested an enteroenteric intussusception.

Surgical intervention showed invagination on a Meckel's diverticulum (*figure 3*) and enlarged mesenteric lymph nodes around it. Diverticulectomy was performed and histopathological examination revealed inflammation and ulcerations. The postoperative course was uneventful and after eight weeks the patient was asymptomatic.

Intussusception represents a rare form of bowel obstruction in adults, accounting for 1-5% of intestinal obstructions.[1] It is defined as the telescoping of a proximal segment of the gastrointestinal tract into the lumen of the adjacent distal segment. According to its location, intussusception can be classified into entero-enteric, if confined to the small bowel, colo-colic, involving the large bowel and ileo-colic, defined as prolapse of the terminal ileum within the ascending colon. It can also be classified by aetiology in benign, malignant or idiopathic.[1] Small bowel intussusception in adults is mostly secondary to intra-luminal pathologies: neoplasms, inflammatory lesions and, rarely, Meckel's diverticula.[1]

Meckel's diverticulum is the most common congenital malformation of the gastrointestinal tract (estimated prevalence 2-4%) and it results from incomplete obliteration of the vitello-intestinal duct.[2] Meckel's diverticula are often discovered incidentally, especially in adults during abdominal exploration.

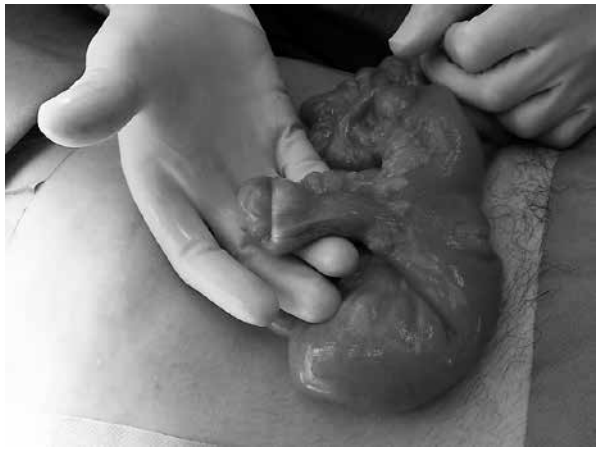
In this case, prophylactic diverticulectomy remains controversial. Park *et al.* recommend resection if there is a risk of a Meckel's diverticulum becoming symptomatic (i.e. age < 50 years, male sex, length of the Meckel's diverticulum > 2 cm and detection of abnormal features inside the diverticulum).[3] Conversely, Zani *et al.* suggest a conservative approach, since resection would unnecessarily expose patients to a higher risk of postoperative complications.[4] Currently, the recommendations are based on authors' experience and single-centre series, and little is known about long-term complications of incidental Meckel's diverticula left in situ.

When symptomatic, Meckel's diverticula present with symptoms of gastrointestinal obstruction or lower gastrointestinal bleeding.[2] Gastrointestinal obstruction is the most frequent complication in adults while children mainly present with bleeding, due to ectopic gastric mucosa.[2] Obstruction may result from intussusception, volvulus, diverticulitis or ulceration. Gastrointestinal bleeding can be chronic and lead to iron deficiency anaemia.[2]

Malignancy within a Meckel's diverticulum has been described in literature and is considered to be rare. Neuroendocrine tumours, leiomyosarcomas, gastrointestinal stromal tumours and adenocarcinomas have been reported.[5-8] Whether risk of cancer should affect management of asymptomatic Meckel's diverticula is unclear.[9,10]

Preoperative diagnosis of Meckel's diverticula is challenging and features on abdominal CT may aid in establishing the diagnosis. Even if unusual, this condition should be considered in the differential diagnosis of abdominal pain and anaemia in young adults.

Figure 3. *Surgical procedure showing invagination of a Meckel's diverticulum*



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ANSWER TO PHOTO QUIZ (PAGE 431)

A LUNG CANCER PATIENT WITH PAINFUL FINGERS

DIAGNOSIS

The X-ray examination showed complete destruction of the bone of the distal phalanx of the fourth digit of the right hand and substantial osteolysis of the distal phalanx of the first and third digit of the left hand. A specimen of the lesion of the third digit of the left hand, obtained through needle aspiration, confirmed the suspicion of a metastasis of the known squamous cell carcinoma. He was treated with a single dose of radiotherapy to relieve the pain, but because of his deteriorating overall clinical condition and the poor prognosis no further treatment was given.

Bone metastases are frequently seen in patients with malignancies, but metastases distal to the elbow and the knee (acrometastases) are rare, accounting for approximately 0.1% of all cases.[1] Primary tumours most frequently associated with acrometastases are lung carcinomas (accounting for 44% of acrometastases) followed by renal cell and breast carcinomas.[1] Acrometastases are associated with a poor prognosis as they mainly occur in patients with disseminated disease.[2] A high index of suspicion is necessary to avoid missing the diagnosis or mistaking it for a more benign condition. Diagnosis can be difficult as pain, swelling, erythema and limited range of motion of joints can be seen in a lot of other, more common, diseases such as osteomyelitis, gout, septic arthritis or other infectious conditions. Acrometastases may be the first manifestation of an occult malignancy (10-16%), but within a majority the primary tumour is already known.[3]

Acrometastases are twice as common in the hand than in the foot[4] and are usually unilateral, but involvement of both sides is seen in up to 10% of the patients.[2]

The dominant hand and the distal phalanx, specifically the middle finger (28%) and the thumb (21%), are most commonly affected.[2] Men are almost twice as likely to have acrometastases than women. This can be explained by the higher incidence of lung carcinomas in men. There are no standard treatment protocols for acrometastases, but because of the poor prognosis of these patients, treatment is mostly directed at palliation.

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ANSWER TO PHOTO QUIZ (PAGE 432)

A 41-YEAR-OLD MAN WITH AN INCREASED ABDOMINAL GIRTH

DIAGNOSIS

The computed tomography scan revealed a massive covering of the peritoneal cavity with accumulation of mucinous material, most likely to be consistent with the diagnosis of pseudomyxoma peritonei. The mesenterium and the omentum were extensively involved, with scalloping of the liver and spleen. At the lower pool of the caecum there was a mass effect that potentially could be a mucinous tumour of the appendix. A puncture was taken and pathology showed material with a remarkable load of mucus, supporting the diagnosis of pseudomyxoma peritonei, most likely a low-grade disseminated peritoneal adenomucosis. Our patient was referred to a specialised centre for treatment of pseudomyxoma peritonei where he had cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC).

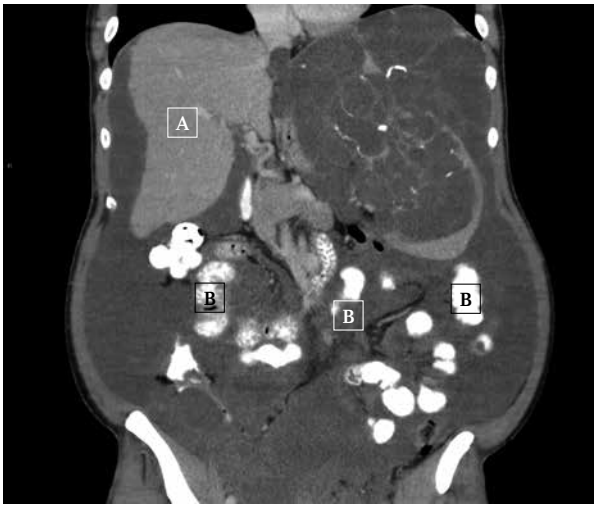
Pseudomyxoma peritonei is a rare condition that originates from a ruptured mucocele of the appendix in the majority of the cases, allowing epithelial cells to redistribute through the peritoneal cavity. In time they will proliferate and produce an excessive amount of mucinous ascites. Histopathologically, pseudomyxoma peritonei can be classified into a low-grade disseminated peritoneal adenomucinosis (DPAM), a peritoneal mucinous carcinomatosis (PMCA), which is the more malignant form, and an intermediate subtype. DPAM is associated with a better prognosis than PMCA. At an advanced stage, patients present with the characteristic distension of the abdomen, the so-called 'jelly belly', eventually leading to intestinal obstruction.[1,2]

Computed tomography of pseudomyxoma peritonei has characteristic features and demonstrates a typical distribution pattern of the mucinous ascites. This can be differentiated from normal watery ascites by density properties. In its end stage, impression of the liver surface ('thumb printing') and compression of the intestines by the mucus can be visualised. Although there are several CT features that are more common in DPAM than in PMCA, and vice versa, there is considerable overlap, which makes radiological differentiation difficult.[3]

Despite differences in biological behaviour and prognosis the current primary treatment is the same for both diseases: cytoreductive surgery followed by an HIPEC procedure. It has an overall ten-year survival rate of 63%. One of the most significant prognostic factors is the degree of extensive and complete cytoreduction. HIPEC contributes predominantly to disease control with a median progression-free survival rate of 8.2 years.[4]

Our patient unfortunately showed early radiological progression, four months after his HIPEC procedure. Therefore he is referred to a gastro-enterologist for further evaluation and potentially additional systemic chemotherapy.

Figure 2. *Abdominal computed tomography with scalloping of the liver (arrow A) and compression of the intestines (arrow B) by the mucinous material*



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LETTER TO THE EDITOR

When to treat paracetamol overdose

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In a recent review, Koppen *et al.* appraised the treatment guidelines for N-acetylcysteine use in NAPQI-mediated paracetamol toxicity.[1] The authors concluded that unlike new UK guidelines, it was unnecessary to lower the current treatment line in the Netherlands. As the authors are aware, the main drive behind the change in UK guidelines comes out of the concern that a small minority of patients below the treatment line remain at risk of hepatic injury. Whether or not this guidance is a cost-effective approach is indeed debatable. However, clinicians need to be acutely aware that there is a spectrum of risk that cannot be easily stratified by a nomogram, which solely considers serum paracetamol level and the time since ingestion. It is already known that younger children and neonates may be at greater risk due to deficient glucuronide conjugation, although this population was not considered in the construction of the original Rumack-Matthew nomogram.[2,3] Furthermore, the nomogram may not adequately guide treatment of overdose with modified-release preparations and also relies heavily on accurate recall of dose timing.[4]

Current guidelines issued by the Dutch National Poisoning Information Centre (NVIC) recommend N-acetylcysteine treatment at a lower serum paracetamol level of 75 mg/l at four hours post-ingestion for certain patients at high risk of hepatotoxicity, such as those with chronic liver disease or malnutrition. Whilst this is lower than the current UK treatment line which starts at 100 mg/l, the Commission on Human Medicines has found that risk factor assessment may be poorly carried out and many known risk factors are imprecise and difficult to assess clinically, particularly in the acute setting.[5] In particular, a clinical history is unreliable when paracetamol overdose is combined with alcohol consumption, other drugs of abuse or a psychiatric history, as is often the case. It is perfectly conceivable that an initial assessment may miss some patients with a severe glutathione deficiency state and pre-existing liver disease who are taking hepatic enzyme inducers. These patients may require treatment even if not indicated by clinical guidance. As a result, there is a risk of delaying treatment when there is a clear time-sensitive benefit in early administration of N-acetylcysteine. UK guidelines have aimed to simplify the decision to treat by utilising a single treatment line which seeks to remove the need to assess for the risk factors of hepatotoxicity.

Regardless of where the treatment line is set, a clinical judgement remains an absolute necessity with current evidence supporting rapid empirical treatment in cases of uncertainty. Additionally, the authors suggest that the main drawback of UK guidelines will be the overtreatment with N-acetylcysteine which would potentially lead to an increased incidence of adverse effects. However, where the treatment line is set should be informed solely by the attendant risk of hepatotoxicity and should not be guided by the side effects of N-acetylcysteine, which whilst common are rarely serious. This is reflected by the recent change in UK guidelines which removed hypersensitivity as a contraindication to N-acetylcysteine treatment. Currently, there are no specific contraindications to N-acetylcysteine treatment of paracetamol overdose in the UK.[5]

It is important to be wary of the small minority of at risk patients who fall below the treatment line. A number of case reports have described patients who failed to receive N-acetylcysteine treatment due to a serum paracetamol level below the treatment line, who subsequently died of fulminant hepatic failure.[6] Despite the additional high-risk treatment line used in the Netherlands, the patient may not be able to provide an accurate clinical history both in terms of the time since the overdose and the risk factors for hepatotoxicity. Further studies are still needed to explore patient risk factors besides serum paracetamol level at a given time, as well as to guide the specifics of N-acetylcysteine treatment, namely the dose, route of administration and treatment duration.

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REPLY

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We appreciate the comments regarding our recommendations of the guidelines for N-acetylcysteine treatment in case of paracetamol intoxications.

We fully agree that there is a spectrum of risk which is difficult to stratify by a nomogram based on serum plasma levels and time of ingestion, and that a nomogram is merely a tool in the clinical decision-making process. Clinicians need to be aware of the different risk groups of patients who cannot be simply treated based on the 150 mg/l nomogram line. We therefore recommend N-acetylcysteine treatment at lower paracetamol plasma values for patients with chronic alcohol abuse, liver insufficiency, malnutrition and/or dehydration and with co-ingestion of medication that might interfere with paracetamol metabolism. In addition, when the time of ingestion is not certain, we recommend N-acetylcysteine treatment. When glucuronide conjugation is not yet optimal, especially in prematurely born children and neonates, N-acetylcysteine treatment at lower plasma concentrations may also be indicated. However, also in very young children, total paracetamol elimination is comparable with that in adults, regardless of the reduced glucuronidation. In fact, children between 1-5 years are less susceptible to paracetamol toxicity.[1]

Using a nomogram and consciously deciding upon the best treatment strategy for an individual patient with paracetamol poisoning will always remain the cornerstone of good clinical practice. Good clinical practice in our view also includes preventing patients from being overtreated.

We agree that possible side effects of N-acetylcysteine should never be a reason to withhold N-acetylcysteine treatment, since the beneficial effects of N-acetylcysteine outweigh its side effects. As the side effects of N-acetylcysteine in general are not that severe, in that regard, overtreatment is not likely to cause major problems, although several UK studies have shown that (mild) side effects are quite common.[2] If treatment was actually unnecessary, that is a burden to the patient. Besides, sending patients to hospital for further evaluation and treatment tremendously increases healthcare costs. As we also mention in our review, the estimation regarding costs for each saved life when the nomogram line is adapted from 150 mg/l to 100 mg/l is around £ 17.4 M (€ 21 M).[3]

We firmly believe that the current Dutch nomogram is of good value in the clinical decision-making process and provides adequate guidance for the optimal treatment strategy in individual patients.

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