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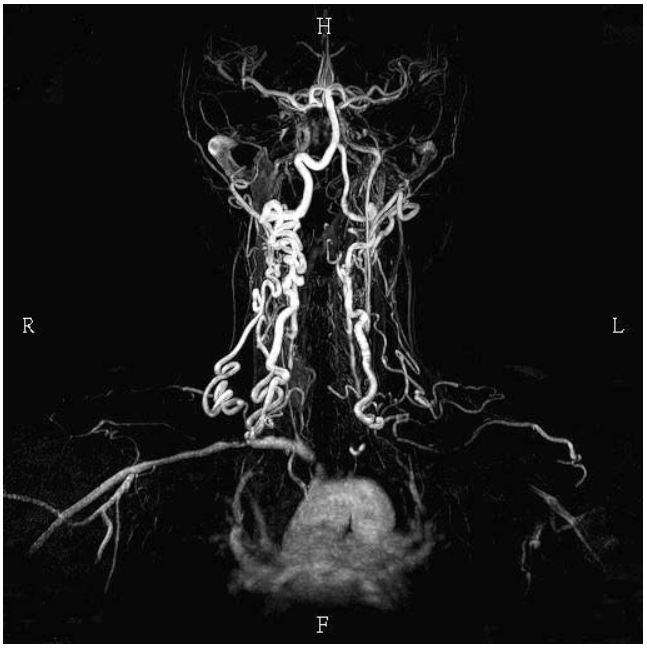

PHOTO QUIZ: Severe arch vessel disease, see page 91

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EDITORIAL

Risk of infectious complications during anti-TNFα therapy

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Tumour necrosis factor α (TNFα) is one of the cytokines that play an active role in inflammatory processes. The observation that TNFα was of major importance for the continued synovial inflammation in patients with rheumatoid arthritis (RA) and that blockade of TNFα decreased arthritis activity in animal models has stimulated the development of TNFα inhibitors for human use. The introduction of these agents has benefited many patients with rheumatoid arthritis. Meanwhile, TNFα inhibitors have also been licensed for the treatment of patients with Crohn's disease, psoriasis, psoriatic arthritis, and ankylosing spondylitis. In the near future the list of indications for this therapy may grow since promising therapeutic effects have been described in patients with sarcoidosis and uveitis.[1,2]

At present three TNFα inhibitors are available for use in daily clinical practice: infliximab, adalimumab, and etanercept. These agents differ in pharmacokinetics and mechanism of action. Infliximab is a chimeric (human-murine) monoclonal anti-TNFα antibody. It is administered intravenously in a dose of 3 to 5 mg/kg bodyweight once every six to eight weeks. Adalimumab is a recombinant fully humanised monoclonal anti-TNFα antibody, which is given subcutaneously in a dose of 40 mg every two weeks. Etanercept is a recombinant soluble p75 TNF-receptor:Fc fusion protein which is administered subcutaneously in a dose of 50 mg once weekly. These differences reflect the differences in duration of action. The half-lives of infliximab and adalimumab are 8 to 10 days and 10 to 20 days, respectively, whereas etanercept has a shorter half-life of four days.[3]

There are subtle differences in the mechanism of action. The TNFα antibodies (infliximab and adalimumab) are more effective in lowering TNF activity, in eliminating macrophages and monocytes, and in reducing γ-interferon production than etanercept.[3] As such, granuloma formation is inhibited to the largest extent by infliximab and adalimumab.

All three TNFα inhibitors have been licensed for the treatment of patients with RA, who have active disease despite treatment with conventional disease modifying antirheumatic drugs such as methotrexate or sulfasalazine. Although head-to-head comparisons are lacking, the agents seem to have similar efficacy for the treatment of patients with RA. In contrast, both monoclonal antibodies are effective in patients with Crohn's disease whereas etanercept, the recombinant soluble receptor, is not. It is tempting to attribute these differences to the abovementioned differences in effect on granuloma formation.

The cytokine TNFα plays an important role in the body's defence against the invasion of micro-organisms by stimulating the recruitment of macrophages and leucocytes to the site of inflammation. As discussed, TNFα also plays a role in the formation of granulomas, a host defence mechanism against intracellular micro-organisms such as *Mycobacterium tuberculosis*. These actions of TNFα suggested that its blockade may lead to a higher incidence of (serious) infections including predominantly those with intracellular micro-organisms. Indeed, the use of TNFα blockers has been associated with the development of granulomatous infections.

Of these, infections caused by *Mycobacterium tuberculosis* are reported most frequently. There is a special predominance of extrapulmonary forms of tuberculosis, as highlighted by the two cases in the report by Verhave *et al.* in this issue of the Netherlands Journal of Medicine.[4] The authors describe two patients with RA who both developed tuberculous peritonitis after starting treatment with the TNFα inhibitor infliximab. These cases underline the difficulties related to the screening of patients for latent tuberculosis, the importance of preventive measures, and the problems in the diagnosis of extrapulmonary tuberculosis. It is well advised to consider

tuberculosis as diagnosis in anti-TNFα treated patients with unexplained symptoms, and in individual cases a blind start of tuberculostatic treatment may be warranted. As pointed out by the authors, the incidence of tuberculous infections is higher during treatment with infliximab (or adalimumab) than with etanercept. This also holds for other granulomatous infections as shown in *table 1*.

Table 1. *Number and incidence of granulomatous infections in patients with rheumatoid arthritis treated with TNFα blockade*[3]

Infection	Infliximab	Etanercept
	n (n/100,000 treated patients)	
Tuberculosis	106 (54)	32 (28)
Histoplasmosis	37 (19)	3 (2.7)
Atypical mycobacteriosis	22 (11)	7 (6.2)
Candidiasis	20 (10)	6 (5.3)
Aspergillosis	17 (8.6)	7 (6.2)
Listeriosis	17 (8.6)	1 (0.88)
Cryptococcosis	10 (5.1)	8 (7.1)
Coccidioidomycosis	11 (5.6)	1 (0.88)
Nocardiosis	7 (3.6)	1 (0.88)
Toxoplasmosis	4 (2.0)	(0)
Total	*255 (130)*	*68 (60)*

The recognition of an increased risk of tuberculosis during anti-TNFα therapy has resulted in the development of a guideline by the Dutch Society for Rheumatology concerning the necessary screening procedures to detect active or latent tuberculosis in these patients before starting therapy.[5] As reflected by the two patients in the case report, foreign-born migrants may be at particular risk. The prevalence of active tuberculosis in immigrants from countries with a high incidence of tuberculosis is <1%. However, the prevalence of latent tuberculosis, defined as a positive tuberculin skin test without chest radiographic abnormalities, may be as high as 35 to 42%.[6] Travel to areas with a high incidence of tuberculosis poses a risk. This has been addressed in a study from the Netherlands which documented that the risk of developing a positive tuberculin skin test was related to the total time spent in the high incidence area. Increased risk was limited to persons who had been travelling for longer than three months.[7]

What about other infectious complications? The early controlled clinical trials with infliximab, adalimumab or etanercept could not document a significantly increased risk of infectious complications.[8-10] However, these clinical trials primarily addressed the efficacy of TNFα inhibitors in RA, and were certainly not powered to detect an increased risk of infection. Studies that are used for the registration of new drugs have important weaknesses with respect to the detection of infrequent, late occurring severe side effects.[11]

The interpretation of the early controlled studies that incorporated evaluation of infectious complications in patients with RA is further complicated by the presence of confounding factors that influence the risk of development of infections such as disease activity, comorbidity, and use of concomitant immunosuppressive drugs. It is well-known that treatment with steroids is an important risk factor for development of infectious complications, a relation which is dose-dependent. Furthermore, Doran *et al.* showed that RA patients not treated with biologicals (and after adjustment for steroid use) were at increased risk to develop infections compared with matched non-RA controls.[12] This means that the disease itself and/or the use of other drugs with immunosuppressive effects could explain the higher infection rate.

Although the abovementioned clinical trials could not document a relation between infections and TNFα inhibition, there are data to support an association between anti-TNFα therapy and the development of serious infections, defined as infections that require antimicrobial therapy or hospitalisation. The most important evidence comes from a large meta-analysis of randomised placebo-controlled trials that included RA patients receiving treatment with infliximab or adalimumab.[13] This meta-analysis compared 3493 RA patients treated with a TNFα inhibitor and 1512 control patients. The relative risk for a serious infection was 2.0 in the patients treated with infliximab or adalimumab.

Data from national registries in which patient cohorts with and without anti-TNFα therapy were compared also suggest an increased risk of infections. An overview of the German registry, including 512 patients treated with etanercept and 346 patients treated with infliximab, showed that the risk of serious infections was significantly elevated during treatment with a TNFα inhibitor.[14] Although the British registry, with data on 7664 anti-TNF treated RA patients, could not document an overall increased risk of infections, there was a relative risk of 4.3 for the development of serious skin and soft tissue infections.[15] The data from the British registry confirmed the particular risk of infections with intracellular bacteria. Infections caused by *Mycobacterium tuberculosis, Legionella pneumophilia, Listeria monocytogenes* and *Salmonella* were exclusively observed in anti-TNF treated patients.

In view of an expected increased risk of postoperative wound infections in patients treated with TNFα inhibitors it is recommended to discontinue these agents temporarily in the perioperative period. The guideline of the Dutch Society for Rheumatology advises withholding TNFα inhibitors preoperatively. The agents should be stopped

to allow disappearance of the drug before the operation, i.e. the time period should be approximately four times the half-life of the particular agent.[16] However, this policy is under debate since there are discussions on the risk of anti-TNF related postoperative infections. In a retrospective study, den Broeder *et al.* concluded that perioperative continuation of anti-TNFα was not an important risk factor for surgical wound infections.[17] In contrast, Giles *et al.* demonstrated a significant association between infectious complications following orthopaedic surgery and treatment with TNFα inhibitors.[18]

In conclusion, patients who are treated with TNFα inhibitors are at risk for infections. Tuberculosis is the major problem; however, other infections may also occur more frequently. The infection risk is no reason to withhold therapy with TNFα inhibitors; however, the agents should be stopped in case of a suspected serious infection. The perioperative use of these agents is under discussion.

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REVIEW

Cholesterol in end-stage renal disease: the good, the bad or the ugly?

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ABSTRACT

The incidence of cardiovascular disease is markedly increased in patients with end-stage renal disease (ESRD). High serum cholesterol is widely recognised as a cardiovascular risk factor in the general population. However, in patients with ESRD high concentrations of cholesterol are associated with a better survival. This reverse epidemiology is, amongst others, caused by confounding due to malnutrition and chronic inflammation. In this population, treatment with statins to lower the serum cholesterol remains a matter of debate. In ESRD, LDL cholesterol is modified by increased oxidative stress. These altered LDL particles play a pivotal role in the development of atherosclerosis. Treatment with the antioxidant vitamin E has not equivocally been shown to be beneficial in this population. This review tries to put data from literature on dyslipidaemia and oxidative stress in ESRD in perspective.

KEYWORDS

Cholesterol, end-stage renal disease, oxidative stress, statins, vitamin E

INTRODUCTION

Patients with chronic renal failure (CRF) are at increased risk for developing cardiovascular disease (CVD). A decreased glomerular filtration rate (GFR) is recognised as an independent cardiovascular risk factor. The increased cardiovascular risk is already apparent in patients with moderate renal insufficiency (GFR <60 ml/min/1.73m^2), and is most prominent in patients with end-stage renal disease (ESRD).[1-3]

High concentration of serum cholesterol is one of the most widely recognised cardiovascular risk factors. There is overwhelming evidence to support serum cholesterol lowering treatment in patients with increased cardiovascular risk.[4-9] It therefore seems logical to extrapolate these findings of the 'bad' effects of cholesterol to patients with ESRD as well. However, there is some evidence to suggest that higher cholesterol *per se* may not be such an important risk factor in patients with ESRD compared with other subjects with an increased cardiovascular risk. In fact, in some studies in ESRD a low serum cholesterol was associated with increased mortality, suggesting 'good' effects of higher cholesterol levels on survival rate.[10,11] Furthermore, a recent randomised trial reported no benefit from therapy lowering serum cholesterol in diabetic haemodialysis patient.[12]

The dispute on cholesterol in patients with ESRD has become even more complicated since low-density lipoprotein (LDL) particles in these patients may be altered, and become 'ugly' through increased oxidative stress, which is characteristic for dialysis patients. This results in the formation of small, dense, oxidised LDL particles that are considered to be highly atherogenic and therefore play an important role in the development of atherosclerosis.[13,14]

In this review, we summarise the data on serum cholesterol as a possible cardiovascular risk factor and the effect of treatment with statins on cardiovascular outcome in patients with ESRD. We put these data in perspective and discuss increased oxidative stress in more detail as a potentially important modifier.

CARDIOVASCULAR RISK PROFILE IN ESRD

Cardiovascular morbidity and mortality in ESRD

Despite the availability of sophisticated techniques for renal replacement therapy (haemodialysis, peritoneal dialysis,

and renal transplantation), life expectancy of patients with ESRD on haemodialysis (HD) and peritoneal dialysis (PD) remains poor, with only a moderate amelioration after renal transplantation. The annual mortality rate in the dialysis population is about 20%. Approximately 50% of these deaths are caused by CVD. This makes cardiovascular mortality 10 to 30 times more prevalent in patients with ESRD compared with the general population.[15]

The poor cardiovascular outcome in patients with ESRD is attributed to an increased incidence and prevalence of CVD as well as a high case fatality rate. In patients treated with HD or PD, the prevalence of overt coronary artery disease (CAD) is approximately 40%.[15] After a cardiovascular event, survival in ESRD is poor: in patients with ESRD mortality rates after a myocardial infarction have been reported to be 59 and 90% after one and five years respectively.[16]

The increased prevalence of CVD is not restricted to patients with ESRD, but is already apparent in patients with mild to moderate renal insufficiency.[17-21] Thus, the process of atherosclerotic CVD starts long before patients reach ESRD. Moreover, it is important to realise that the arterial lesions in patients with ESRD differ from those observed in patients with classical coronary artery disease.[22,23] In patients with classical atherosclerotic disease, the vascular plaques have the typical aspects of atheromatous or fibroatheromatous plaques, with a prominent presence of lipid accumulation. In contrast, patients with ESRD have typical calcified plaques, predominantly composed of fibrous tissue and calcium deposits.[23] Furthermore, thickening of intima and media of the vessel wall, with subsequent narrowing of the lumen, is more prominent in ESRD. In addition to atherosclerotic or calcified vascular disease, patients with ESRD are more prone to the development of left ventricular hypertrophy (LVH) as a result of hypertension and anaemia. Both tissue calcification and LVH contribute to the development of myocardial fibrosis, diastolic dysfunction and left ventricular conduction abnormalities. This not only leads to heart failure, but more importantly may predispose to potentially lethal primary cardiac rhythm disturbances.[22-24] Notably, although mortality in patients with ESRD is often attributed to CVD, many patients die suddenly with presumed cardiac arrest, and only a minority die from typical atherosclerotic diseases such as myocardial infarction or stroke. This is reflected by data from the recent USRDS registry, showing that in 2005, 7.2% of dialysis patients died from cardiac arrest or cardiac arrhythmia whereas myocardial infarction or coronary heart disease were the cause of death in 2.9% of the patients.[25]

Cardiovascular risk factors in ESRD

In discussing cardiovascular risk factors in patients with ESRD, a distinction can be made between traditional and nontraditional risk factors. The traditional risk factors are defined by epidemiological studies such as the Framingham study and influence the development of CVD in the general population. These risk factors may also be applicable to the dialysis population. The CHOICE study showed that the majority of dialysis patients had one or more of the traditional cardiovascular risk factors: 54% of the patients had diabetes mellitus, 33% had a low serum HDL cholesterol, 96% suffered from hypertension, 22% had left ventricular hypertrophy and the average age of the patients at the start of dialysis therapy was 60 years. Of note, an increased LDL cholesterol (>4.2 mmol/l) was observed in only 11% of patients.[26] Because of the large difference in cardiovascular risk between the general population and patients with CRF and ESRD, it was postulated that in the latter patients additional 'nontraditional' cardiovascular risk factors must be present. Examples of these nontraditional risk factors include calcium, phosphorus, PTH, vitamin D, and CRP.[3,27-30] It has been postulated that these nontraditional risk factors could (partly) explain the large difference in cardiovascular disease between the general and the renal population. Little attention is given to alterations in lipid composition in ESRD.

SERUM CHOLESTEROL IN ESRD

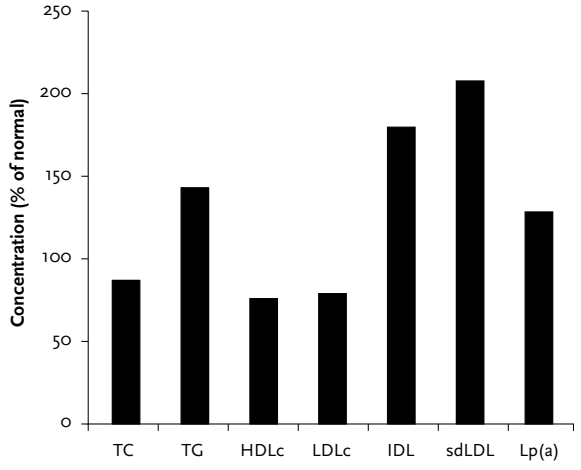
Characteristics of the lipid profile in ESRD

In patients with ESRD, dyslipidaemia is a common finding. This is caused by alterations in the metabolism and the composition of the plasma lipoproteins. The typical, traditional lipid profile in patients with ESRD is characterised by normal or low concentrations of LDL cholesterol, increased concentrations of triglycerides (TG) due to elevated levels of very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) and decreased high-density lipoprotein cholesterol (HDL). The LDL composition is abnormal and characterised by the presence of small dense LDL particles (*figure 1*). There are slight differences between patients treated with haemodialysis and those treated with peritoneal dialysis: levels of LDL cholesterol and small dense LDL are higher and levels of HDL cholesterol are lower in patients on peritoneal dialysis compared with patients on haemodialysis.[27,31-33] Most studies which describe the abnormalities in lipoproteins in ESRD focus on the 'absolute' levels of lipoproteins but do not mention possible alterations in the 'state' of these lipoproteins (e.g. oxidised or carbamylated), which may affect early onset of atherosclerosis.

Impact of dyslipidaemia on cardiovascular disease in ESRD

Several studies reported an association between dyslipidaemia and surrogate cardiovascular endpoints. Tamashiro *et al.* described that in chronic haemodialysis patients the progression of coronary arteries calcification

Figure 1. *Lipid abnormalities in patients with end-stage renal disease*[27,31-33]



TC = total cholesterol; TG = triglycerides; HDLc = high-density lipoprotein cholesterol; LDLc = low-density lipoprotein cholesterol; IDL = intermediate-density lipoprotein; sdLDL = small dense LDL; Lp(a) = lipoprotein (a).

was related to high concentrations of TG and low concentrations of HDL.[34] These data were confirmed in peritoneal dialysis patients.[35] Although these studies suggested that dyslipidaemia may affect cardiovascular outcome in patients with ESRD, many studies have failed to find a positive association between the traditional lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) and cardiovascular endpoints in patients with ESRD.[36-39] In fact, these studies often noted a seemingly inverse relationship, low cholesterol levels being associated with higher mortality rates.[10] Although these observations have been used as arguments against a contributory role of cholesterol in cardiovascular disease in patients with ESRD, it is now clear that this 'reverse epidemiology' is explained by the confounding effects of malnutrition and inflammation.

Many patients with ESRD have evidence of malnourishment and chronic inflammation. Clinically these patients are characterised by lower body weight, lower blood pressure, low cholesterol, low serum albumin and elevated CRP. Survival rates are low in these patients. With this in mind it is no surprise that in patients with ESRD the presence of this chronic inflammatory state confounds normal associations and causes reverse epidemiology. Recent studies demonstrate this clearly. Liu *et al.* observed a higher cardiovascular event rate in ESRD patients with low serum cholesterol. However, when restricting the analysis to patients without inflammation and malnutrition they observed the 'normal' positive association between serum cholesterol and CVD mortality.[40] Iseki *et al.* confirmed this by showing that high concentrations of cholesterol were associated with a higher mortality risk in patients with normal serum albumin levels.[10] These studies suggest that in well-nourished, noninflammatory dialysis patients, hypercholesterolaemia is a cardiovascular risk factor.

Reverse epidemiology is only one part of the story. The lack of an association between LDL cholesterol and cardiovascular risk may also be explained by the contributions of other lipoproteins. As mentioned above, in patients with ESRD levels of IDL, small dense LDL and Lp(a) are increased. Several studies have reported a positive association between some of these lipoproteins and cardiovascular disease.

In patients with elevated levels of IDL there is evidence of atherosclerotic disease. Moreover, Shoji *et al.* showed that IDL is an independent risk factor for aortic sclerosis in HD patients.[41] In patients with ESRD Lp(a) is a risk factor for disease and mortality.[42-45] Finally, the highly atherogenic LDL subclass, small dense LDL, is present in HD patients.[32] In ESRD, these 'alternative' lipoproteins may fulfil a more important role in the development of cardiovascular disease than LDL. Therefore, it may be important to also focus on these nontraditional lipid parameters.

Moreover, biochemical modifications of LDL, not reflected by total and LDL cholesterol levels, may offer another explanation for the increased cardiovascular risk in patients with ESRD. The most important process involves the oxidation of lipids (discussed below in more detail).

Effect of treatment of dyslipidaemia in CRF and ESRD with statins

In the general population, treatment with HMG CoA reductase inhibitors or statins is one of the cornerstones in the strategies to reduce cardiovascular risk, both in primary and secondary prevention.[4-9] Since patients with CRF are at a high risk to develop CVD, treatment of all risk factors including serum cholesterol seems warranted. Indeed, most guidelines recommend aggressive treatment of LDL cholesterol. However, treatment with HMG CoA reductase inhibitors in patients with CRF is still open for debate, since for this subgroup the data on effect of treatment are scarce, as most trials excluded patients with severe renal insufficiency. Posthoc subgroup analysis of the Heart Protection Study (HPS) and the Cholesterol Recurrent Events Trial (CARE) indicated that cholesterol lowering was beneficial in patients with moderate renal insufficiency (GFR 30-60 ml/min.[6,46,47] However, few data are available to allow conclusions for patients with GFR <30 ml/min.

What is known about treatment of serum cholesterol in patients with ESRD?

A Cochrane review, published in 2004, concluded that statins decreased serum cholesterol in dialysis patients as effectively as in the general population. With respect

to the effects of statins on (cardiovascular) mortality no conclusions could be drawn because of the lack of studies with hard clinical endpoints.[48]

The effects of lipid-lowering therapy with statins on surrogate endpoints suggested potential benefits. Achenbach *et al*. demonstrated that treatment with cerivastatin reduced the progression of coronary calcium deposition.[49] Few studies have evaluated the effects of statin therapy on cardiovascular endpoints in patients with ESRD. Two uncontrolled studies reported a reduced cardiovascular mortality in patients who had been treated with statins.[50,51] This benefit was limited to patients with a previous history of cardiovascular disease. Although appealing, these data do not allow firm conclusions. Although the authors used multivariate analysis to adjust for known risk factors, confounding could not be excluded. In fact, only 10% of the ESRD patients used a statin, and those patients had higher cholesterol levels and less signs of malnourishment. Thus, the above-mentioned reverse epidemiology might explain the relationship between survival and statin use in these studies

The ongoing Study of Heart and Renal Protection (SHARP) is designed to study the effects of treatment with simvastatin and ezetimibe on cardiovascular disease in patients with chronic renal failure. Biochemical safety and efficacy have been shown.[52,53] The more interesting and important results of this study can be expected after 2007. The AURORA (Assessment of Survival and Cardiovascular Events) study is an ongoing randomised controlled trial, which will evaluate the efficacy of rosuvastatin in preventing cardiovascular events in HD patients.[54] Results of this study can be expected in the coming years.

So far, only one randomised controlled trial has evaluated the effect of treatment with a statin on clinical endpoints in haemodialysis patients.[55] Results of Die Deutsche Diabetes Dialysis study (4D study) were reported in 2005.

The 4D study included 1255 patients with type 2 diabetes mellitus on maintenance haemodialysis therapy. Patients with serum LDL-cholesterol levels between 2.1 mmol/l and 4.9 mmol/l were randomised for treatment with atorvastatin 20 mg or placebo. Primary endpoint was a composite of death from cardiac causes, nonfatal myocardial infarction and stroke. Secondary endpoints included death from all causes and all cardiac and cerebrovascular events combined. Atorvastatin effectively lowered serum cholesterol, was safe and well tolerated. Obviously, a reduction in cardiovascular endpoints was expected in view of the high cardiovascular risk profile of these patients. Disappointingly, treatment with atorvastatin did not significantly reduce the incidence of primary endpoints. The results of this study are often quoted and used as an argument against cholesterol lowering in patients with ESRD. However, it is important to take a closer look at the data. *Table 1* provides data on specific causes of death reported in the 4D study. Mortality was very high in the study population. It is evident that sudden death was more frequent than death from coronary heart disease. Atorvastatin lowered the incidence of death due to coronary heart disease, but had no effect on sudden death. As for the prevention of coronary death, treatment with atorvastatin was associated with an absolute risk reduction (ARR) of 2.2%, with a calculated number needed to treat (NNT) of 45. Admittedly, there was no overall statistically significant survival advantage in the atorvastatin-treated group, which is readily explained by the high incidence of death from nonatherosclerotic disease. Still, the analysis may suggest that also in patients with ESRD statins are able to modify the process of classical atheromatous disease and lower the incidence of classical, atherosclerotic coronary heart disease. In contrast, cholesterol lowering is unlikely to influence myocardial fibrosis and prevent death from cardiac arrhythmias.

Another interesting way of putting the results of the 4D study in perspective is a comparison between the 4D study and the Cholesterol Treatment Trialists' study (CTT), a meta-analysis of 14 randomised controlled trials (RCTs) of statins (*table 2*).[56] Specifically, when focusing on overall mortality and mortality due to coronary heart disease, it can be expected that cholesterol lowering is primarily beneficial by reducing the risk of an ischaemic atherosclerotic cardiovascular event. When calculating the absolute risk reduction of coronary deaths, the results of the 4D study appear comparable with the other studies with an ARR of 2.3% as compared with 0.4 to 3.5% in other studies.

Table 1. *Coronary mortality and sudden death in the Deutsche Diabetes Dialysis study*[12]

		Placebo (n=636)	Atorvastatin (n=619)	ARR	NNT
Cardiac death due to atherosclerotic disease	Death due to CHD	5 (0.8%)	1 (0.2%)		
	Death due to intervention for CHD	4 (0.6%)	3 (0.5%)		
	Fatal MI	33 (5.2%)	23 (3.7%)		
	Subtotal	42 (6.6%)	27 (4.4%)	2.2%	45
Nonatherosclerotic death	Sudden death	83 (13.1%)	77 (12.4)	0.6%	164
Subgroup 1 + 2	Total	125 (19.7%)	104 (16.8%)	2.9%	35

ARR = absolute risk reduction; NNT = numbers needed to treat; CHD = coronary heart disease; MI = myocardial infarction.

Table 2. *A comparison of the mortality due to coronary heart (CTT) disease and any death between the Deutsche Diabetes Dialysis (4D) study[12] and the Cholesterol Treatment Trialists' study[56]*

CTT	**Placebo (n=45,002)**	**Statin (n=45,054)**	**ARR**	**NNT**
Death due to CHD	1960 (4.4%)	1548 (3.4%)	0.9%	109
Any death	4354 (9.7%)	3832 (8.5%)	1.1%	89
4D	**Placebo (n=636)**	**Atorvastatin (n=619)**	**ARR**	**NNT**
Death due to CHD	42 (6.6%)	27 (4.4%)	2.2%	45
Any death	320 (50.3%)	297 (48.0%)	2.3%	43

ARR = absolute risk reduction; NNT = numbers needed to treat; CHD = coronary heart disease.

However, coronary death rate was only a small fraction of total mortality in the 4D study (11%). The overall mortality in the 4D study as well as the percentage of sudden deaths is impressive, whereas the absolute coronary event rate is rather low. One may thus conclude that, with respect to coronary events, the 4D study was clearly underpowered.

Furthermore, benefits of cholesterol lowering may not be expected in patients with the highest risk, i.e. patients with chronic inflammation and malnutrition on dialysis. As mentioned earlier, based on the data of Liu and Iseki, cholesterol lowering might be of benefit in patients with absent inflammation and no signs of chronic inflammation, most likely patients with a higher life expectancy.[10,40] In this respect the survival curve depicted in the CTT is interesting for the reported timeframe of protection. Although benefits of cholesterol lowering were evident within the first year, the effects were greater in subsequent years. Short-term mortality rate is high in patients with ESRD and in particular in patients with diabetic disease or patients with malnutrition and inflammation. Any benefit of statin treatment in patients with ESRD will thus only become apparent after many years, in patients who are well nourished, not inflamed and have a reasonable life expectancy. In this respect, analysis of the survival curves in the 4D study is notable. The survival curves of the placebo and the active treatment groups start to deviate after four years follow-up, indeed suggesting that differences might become evident with longer follow-up. It would be informative to know the state of inflammation and nutrition of the patients included in 4D and its relation with mortality. At baseline 58.6 % of the included patients had LDL cholesterol below 3.4 mmol/l. This is quite low and might be indicative of malnutrition.

Thus, we feel that the data of the 4D study do not allow the general conclusion that ESRD patients do not benefit from statin treatment. It will be important to select patients who will benefit from such therapy. We propose that this selection will include patients with pre-existing CVD and patients with a long life expectance (absence of inflammation and malnutrition). Ongoing large randomised controlled trials such as AURORA and SHARP will hopefully provide some answers and allow a more precise way of decision making in this high risk population.[54,57]

OXIDATIVE STRESS IN ESRD

Background of oxidative stress

Since increased oxidative stress is characteristic for patients on HD and may play an important role in the progression of atherosclerosis in ESRD, we will discuss this topic in more detail.

Oxidative stress can be defined as the result of an imbalance between the production of reactive oxygen species (ROS)/free radicals (FR) and antioxidant defences.[58] Oxidative injury can change the function and structure of biomolecules such as lipids, proteins, carbohydrates and nucleic acids. Oxidised lipids may be involved in the initiation and acceleration of atherosclerosis. Interventions directed at preventing lipid oxidation may have therapeutic potential.

Is oxidation present in ESRD?

In patients with CRF, the balance between pro-oxidant and antioxidant capacity is shifted towards an increased oxidative stress. The pro-oxidant effects are caused by factors that are characteristic for the CRF population, e.g. advanced age, diabetes mellitus, uraemic toxins, chronic inflammation, malnutrition and treatment with dialysis. Moreover, both the intracellular and extracellular antioxidant capacity is decreased because of depletion of selenium, vitamin C, vitamin E and decreased activity of super oxide dismutase and glutathione peroxidase.[59-62]

For a long time, reliable assessment of oxidative stress in CRF has been problematic and the results of different studies were inconsistent. These inconsistencies were most likely caused by the lack of standardised methods to determine the level of oxidative stress.

We assessed oxidative stress in ESRD patients using different methods.[63] First, we measured the susceptibility of circulating LDL particles to copper-induced oxidative stress *in vitro* as described by Esterbauer *et al.*[64] We observed that LDL particles of ESRD patients were not more susceptible for oxidation *in vitro* compared with matched controls. Our findings are in agreement with the observations of other authors.[65,66] Although these findings argue against increased oxidative stress in ESRD, this *in vitro* assay has several drawbacks. The test results may be

influenced by the blood composition of unsaturated fatty acids. In patients with ESRD, levels of monounsaturated fatty acids (MUFAs) but not polyunsaturated fatty acids (PUFAs) are higher than in controls.[65] Since MUFAs are less susceptible to copper oxidation, the increased amounts of MUFAs in ESRD might explain the measured decreased oxidisability in these patients. Furthermore, the test is influenced by several factors such as the blood temperature after collection, the storage temperature, and the levels of triglycerides, and vitamin C and E in the blood. Moreover, the 'oxidative' situation in this *in vitro* assay might not be representative for the situation *in vivo* in the subendothelial space, where the process of atherosclerosis takes place.
We also evaluated oxidation using a more recently developed monoclonal antibody against oxidised LDL. Increased antibody levels are accepted as markers of oxidative stress. We indeed noted increased antibody concentrations suggesting a higher LDL oxidation level in patients with ESRD.[63] Other markers have also been proposed for the assessment of oxidation such as plasma F2-isoprostanes and advanced oxidation protein products (AOPP). Recent studies all provided evidence for increased oxidative stress in CRF.[67-73]

Is there an association between increased oxidative stress and cardiovascular disease in ESRD?
Oxidised LDL particles play a pivotal role in the development of atherosclerosis: these particles are incorporated without restriction by macrophages through scavenger receptors. This promotes accelerated formation of foam cells, which will gradually transform and degrade into plaques, thus contributing to vascular stenoses.[13,74-77] An environment in which enhanced oxidative stress is present will therefore add to the development of atherosclerosis and cardiovascular disease.

In nonrenal patients, Holvoet *et al*. showed that a high level of circulating oxidised LDL particles is a sensitive marker of coronary artery disease.[70] Similar data were found in CRF patients. HD patients with a positive history of atherosclerotic disease have higher oxidised LDL concentrations than patients without a cardiovascular history.[78] Shoji *et al*. investigated the association between antibodies against oxidised LDL and the intima media thickness (IMT) in the carotid and femoral artery. They found that antioxidised LDL antibodies were positively correlated with IMT of the carotid artery.[79] The same authors described that the antioxidised LDL antibody titre is an independent predictor of cardiovascular mortality in patients with ESRD.[80]

Treatment of oxidative stress with vitamin E
Vitamin E refers to a group of eight, fat soluble, naturally occurring compounds, α-,- β-, γ- and δ-tocopherol and α-, β-, δ- and γ-tocotrienols. Of these compounds, α-tocopherol has been found to be the most abundant and active antioxidant of LDL.[81] Gamma-tocopherol is the predominant form of vitamin E in human diets, α-tocopherol is the primary form of vitamin E supplements.

Alpha-tocopherol acts by scavenging reactive oxygen species and singlet oxygen that otherwise would attack biomolecules such as lipids, proteins, sugars and nucleic acids.[82] In the process of lipid peroxidation, lipids react by propagation of a lipid peroxyl radical so that a lipid radical and lipid hydroperoxide are formed. Alpha-tocopherol scavenges the lipid peroxyl radical before it attacks its substrate (lipids). In this reaction, the lipid peroxyl radical is neutralised to lipid hydroperoxide and (the neutral) α-tocopherol is formed into a stable α-tocopherol radical which does not propagate radical chains and lipid peroxides. Moreover, vitamin C can donate an electron to the α-tocopherol radical so that α-tocopherol can be regenerated. In this way, the weak antioxidant vitamin C can enhance the antioxidative effects of vitamin E.
Alpha-tocopherol scavenges the peroxyl radical about ten times faster than the lipid reacts with the radical. Therefore, α-tocopherol prevents lipids from being modified by peroxyl radicals.

It is generally accepted that patients with CRF and ESRD suffer from increased oxidative stress resulting in increased lipid peroxidation. This is one of the contributing factors to the accelerated atherosclerosis in this population.

Himmelfarb *et al*. studied the α- and γ-tocopherol metabolism in patients with ESRD.[83] They found that serum α-tocopherol levels were similar between haemodialysis patients and controls. However, the levels of serum γ-tocopherol were higher in haemodialysis patients. This finding suggests that renal failure influences the γ-tocopherol metabolism. The metabolites of both α- and γ-tocopherol, α- and γ-carboxyhydroxychromans (CEHC) were tenfold and sixfold higher in haemodialysis patients compared with healthy subjects, respectively. These results confirm the role of urinary excretion of the water-soluble metabolites of tocopherol in subjects with normal renal function.

The observation that increased oxidative stress may contribute to progressive atherosclerosis has stimulated searches for antioxidant therapies.
It has been hypothesised that treatment with vitamin E can prevent the oxidative modification of LDL and in this way attenuate the development of atherosclerosis and cardiovascular disease. However, the results of studies on this subject are conflicting.
A meta-analysis by Vivekananthan *et al*. included 15 randomised controlled trials, seven evaluating the effects

of vitamin E and eight evaluating β-carotene.[84] The studies with vitamin E contained 81,788 patients from different populations, most with normal renal function. Both primary and secondary prevention trials were pooled. No beneficial effects of vitamin E were found. A similar conclusion was reached in an earlier meta-analysis by Asplund.[85] Moreover, data published by Miller *et al.* suggested that high-dosage vitamin E supplementation might unexpectedly increase all-cause mortality.[86]

What is known about the treatment with vitamin E in patients with chronic renal failure and ESRD?

Many studies on surrogate endpoints with vitamin E have been performed on ESRD.[87-92] These studies range from treatment with oral supplementation of vitamin E to treatment with vitamin E coated artificial kidneys. A problem in comparing and interpreting these studies is that the results are conflicting, probably as the result of the lack of uniform methods to assess oxidative stress.

In a post-hoc analysis of the Heart Outcome Prevention Evaluation study (HOPE), 993 patients with mild-to-moderate renal failure were analysed.[93] Primary endpoints were defined as the composite of myocardial infarction, stroke or cardiovascular death. Secondary endpoints included revascularisation, total mortality and clinical proteinuria. Treatment with 400 IU vitamin E once daily did not result in reduction of primary or secondary endpoints after an average follow-up of 4.5 years.

Thus far, the only RCT with vitamin E on hard clinical endpoints has been performed by Boaz *et al.*[94] The Secondary Prevention with Antioxidants of Cardiovascular disease in End stage renal disease (SPACE) showed that in 196 haemodialysis patients with known cardiovascular disease, supplementation with 800 IE/day of vitamin E reduced the risk on composite cardiovascular endpoints and myocardial infarction. This study suggests that vitamin E may be effective in patients with ESRD, and the differences with other studies could be explained by the higher grades of oxidative stress in ESRD. Although the results seem convincing, there are some caveats. Overall mortality was not influenced. Furthermore, the population in the study is somewhat different from the normal ESRD population as reflected by a rather low sudden death rate. Apparently, the authors have included a population at low risk for nonatherosclerotic death. Notably, although many patients had experienced a previous myocardial infarction or cerebrovascular accident, less than 50% of the patients were treated with aspirin. Since the results of SPACE were mainly driven by the difference in myocardial infarctions, it needs to be proven that similar benefits would have been obtained if all patients had received aspirin. Therefore, although the results of the SPACE study are very appealing they should be confirmed in a new study with noncomposite cardiovascular endpoints.

CONCLUSIONS

Cardiovascular risk is increased in patients with CRF, and is particularly high in patients with ESRD. However, in patients with ESRD cardiovascular mortality is not primarily the consequence of classical coronary heart disease but more often caused by sudden cardiac death. The latter is likely related to rhythm disturbances due to cardiac fibrosis and hypertrophy. In patients with CRF both traditional cardiovascular risk factors such as hypertension, diabetes mellitus, smoking, hypercholesterolaemia and nontraditional risk factors such as increased oxidative stress, malnutrition, disturbed calcium-phosphate balance and hyperparathyroidism contribute to the increased risk

Although cholesterol-lowering treatment is generally effective in patients with increased CVD risk, the evidence is lacking in patients with ESRD. The absence of proof should not lead to therapeutic nihilism. Interpretation of the data is hampered by reverse epidemiology in patients with ESRD, the high mortality rate due to nonatherosclerotic disease and malnutrition and inflammation. We would argue that cholesterol lowering should be considered in patients with known CVD and patients with ESRD without evidence of malnutrition and inflammation and a life expectancy of more than five years. Obviously, apart from cholesterol, treatment in patients with ESRD should be directed at optimising all other risk factors such as hypertension, calcium-phosphate balance, vitamin D and hyperparathyroidism. The role of influencing altered lipids in ESRD is unclear.

Randomised controlled trials that are underway will hopefully assist in further defining the population at risk who will benefit from interventions directed at cholesterol. In the meanwhile, treatment of patients with ESRD should be multitargeted. Also in this population cholesterol should not be an overlooked target.

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REVIEW

Generics: what is the role of registration authorities

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ABSTRACT

Substitution of branded medicines by cheaper generic medicines has been and is subject for debate in the Netherlands. One of the tasks of the Dutch Medicines Evaluation Board (CBG) is the evaluation of generic medicines. The way the CBG approves generics, as outlined in this paper, is based on assessment of the quality of the medicine and bioequivalence testing according to strict European guidelines. Registration of generic medicines in the Netherlands will only take place when bioequivalence has been demonstrated. Once bioequivalence has been demonstrated, the CBG is convinced that the generic has the same efficacy and safety as the branded medicine. Consequently, the CBG is of the opinion that the branded medicine can be safely exchanged with the generic medicine. However, for the acceptance of generics in daily practice adequate communication to the patient by prescriber, pharmacist, health insurance company and patient organisations is essential.

KEYWORDS

Branded medicines, generic medicines

INTRODUCTION

To constrain public health costs, the policy of the Dutch government and the health insurance companies is to substitute the more expensive innovator (brand-name) medicines by cheaper generic medicines. For many years, this generic substitution has been the subject of debate in the scientific literature.[1-11] The Dutch Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen, CBG) is not directly involved in the actual substitution strategy in the Netherlands, but the registration of generic medicines in the Netherlands will only take place when the CBG is convinced that the generic has the same efficacy and safety as the innovator medicine. As our contribution to the discussion on generic substitution, we felt it would be useful to elaborate on how the CBG approves generics based on assessment of the quality of the medicine and bioequivalence testing. The CBG has started to publish public assessment reports for generics on its website (http://www.cbg-meb.nl/nl/gnsmiddl/index.htm).

A generic is a medicinal product which has the same qualitative and quantitative composition of active substances and the same pharmaceutical form as the branded product. In other words, the generic is a pharmaceutical equivalent to the branded medicine. A company may seek marketing authorisation for a generic in the Netherlands ten years after a marketing authorisation has been issued for the innovator medicine in one of the EU States. The original preclinical and clinical data are then no longer legally protected and the generic company may refer to the file of the innovator medicine for those data.

REGISTRATION OF GENERIC MEDICINES BY THE CBG

The application for a generic medicine is based on a complete chemical-pharmaceutical file, similar to that used when applying for registration of the branded medicine, thus ensuring a good quality medicine as well on adequate bioequivalence testing. As the active substance's efficacy and safety have been well established for the innovator medicine, it is generally not required to provide results of preclinical tests in animals and of clinical trials with a generic application. Instead, a study is necessary to establish

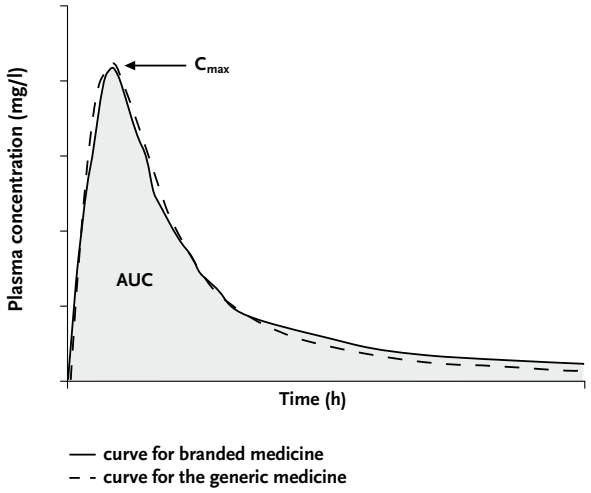
equivalence between the generic and brand-name medicine to prove that differences in excipients and/or the manufacturing process do not affect the absorption characteristics of the active substance. This is known as a bioequivalence study. The requirements for demonstrating bioequivalence are outlined in European Guidelines.[12-15] The European guideline 'NfG on the investigation of bioavailability and bioequivalence (CHMP/EWP/QWP/1401/98)' forms the basis for the assessment of generics with a systemically acting active substance.[12] This guideline typically deals with medicinal oral formulations with immediate-release characteristics.

Bioequivalence is generally determined by comparing the time course of the plasma concentration of the active substance after a single administration of the generic and the innovator medicine in a two-way cross-over study in healthy volunteers. The design of bioequivalence studies is standardised in order to minimise the variability of all the factors involved, so that the effect of the formulation on plasma exposure can be distinguished from other effects. The number of subjects required, usually 24 to 36 subjects, depends on the variability of the pharmacokinetics of the active substance.

Bioequivalence studies are conducted according to the principles of Good Clinical Practice (GCP) and Good Laboratory Practice (GLP). These requirements are the same worldwide, whether in Western countries or in *'low cost'* countries. The same criteria that apply for GCP and GLP in the European study centres also apply for these low-cost study centres, and these centres are also subjected to inspection by the various European States.

Bioequivalence is aimed at demonstrating identical plasma exposure over time. Critical parameters used to demonstrate this are the extent of absorption of the active substance (as measured by the area under the concentration time curve (AUC)) and the rate of absorption (as measured by the maximal plasma concentration (Cmax)) (*figure 1*). The individual test/reference ratio (generic/innovator) is calculated for the (log-transformed) AUC and Cmax values. Subsequently a 90% confidence interval for the mean ratio is calculated for both AUC and Cmax. When the 90% confidence interval of the test/reference ratio is within the 0.80 to 1.25 interval for both AUC and Cmax, it is concluded that the generic and branded product are bioequivalent with respect to the rate and extent of absorption of the active substance. After a long international discussion it was decided that a 0.80 to 1.25 90% confidence interval ensures that possible differences in formulation due to excipients and/or the manufacturing process between the generic and branded product do not affect the systemic exposure of the active substance to a clinically relevant extent. The same 90% confidence interval is used when innovator companies decide to change their formulation during development or marketing of their products. Consequently, if bioequivalence is demonstrated within the 90% confidence interval, the positive benefit risk established in clinical studies for the branded medicine also applies for the generic.

Figure 1. *Illustration of plasma concentration-time curves from a bioequivalence study*



AUC is the marker for the extent of absorption and C_{max} for the rate of absorption of the active substance.

SPECIAL FORMULATIONS

When a generic concerns a product with controlled or delayed-release characteristics (e.g. long-acting or slow-release medicines), additional studies are required as is outlined in a European guideline on modified release products.[14] For such formulations, bioequivalence should generally be demonstrated both after single dose and after multiple dose administration. In that case, it is not only the rate and extent of absorption that are critical parameters, but also the trough concentration (Cmin) and peak-trough fluctuations need to be taken into account for concluding bioequivalence. Furthermore, for oral formulations with regulated release characteristics, bioequivalence should not only be demonstrated under fasting conditions but also under fed conditions in order to examine a known food effect or to exclude dose dumping and/or instability of the product.

For dermal patches, which can be considered a regulated-release product, the generic should not only demonstrate bioequivalence as indicated for oral formulations, but also the same or less adhesiveness to the skin, sensitisation and local irritation compared with the branded product. The precise type and number of studies to be performed for generic products with controlled-release characteristics is defined on a case by case basis taking into consideration the intrinsic properties of the active substance, the route of administration, the type of delivery system and the intended therapeutic indication(s).

SPECIAL CIRCUMSTANCES

Low absolute bioavailability

In some cases the systemic absorption of the active substance is so low that plasma levels cannot be measured reliably. This has been reported for e.g. alendronate (Fosamax). Due to its low absolute bioavailability of only 0.6%, the plasma concentrations hardly exceed the detection limit. Since alendronate is almost exclusively excreted unchanged in the urine, the amount excreted in the urine is directly related to the plasma AUC. Thus, the amount excreted in the urine can be used as a measure for the extent of absorption, instead of the plasma AUC value.[12,13] Analogously, the rate of absorption can be determined using the rate of excretion. It is acknowledged that this rate of excretion can be determined somewhat less accurately in urine than in plasma because of the less frequent sampling of urine. Therefore, to ensure that the rate of absorption does not differ essentially, additional comparable *in vitro* dissolution under various conditions is required for these alendronate applications. With recent improvements in the sensitivity of alendronate analytical assays, the generic application for the 70 mg, high-dosage form of alendronate can be based on the urine measurement for the amount absorbed, combined with the plasma Cmax as an accurate measure for the rate of absorption. With this procedure efficacious and safe generic products for alendronate can be registered.[12,13]

Locally acting drugs

For locally applied medicines, which exert their effect at the site of application, the common systemic bioavailability approach cannot be applied because the plasma concentration in such a case is not representative for its efficacy. Examples are certain dermatological products and inhalation products. Registration of these generic products based on bioequivalence testing is in principle not possible and therapeutic equivalence needs to be demonstrated using pharmacodynamic endpoints or clinical studies.[15]

Although efficacy of these products is dependent on local exposure, often a small fraction of the dose reaches the systemic circulation which may thus exert undesired effects. For this reason a comparative bioavailability study can be supportive for the safety of the generic product.

One exceptional case of a locally acting drug is mesalazine, which is indicated for ulcerative colitis and Crohn's disease. Despite the local action in the intestinal tract, a generic has been registered in the Netherlands supported by systemic bioequivalence studies. The reason for this is that on the basis of the plasma concentration time course of mesalazine and its metabolite, the site of absorption of mesalazine can be assessed. This means that indirectly the local availability of mesalazine in the relevant parts of the intestine is known and can be compared.[16,17]

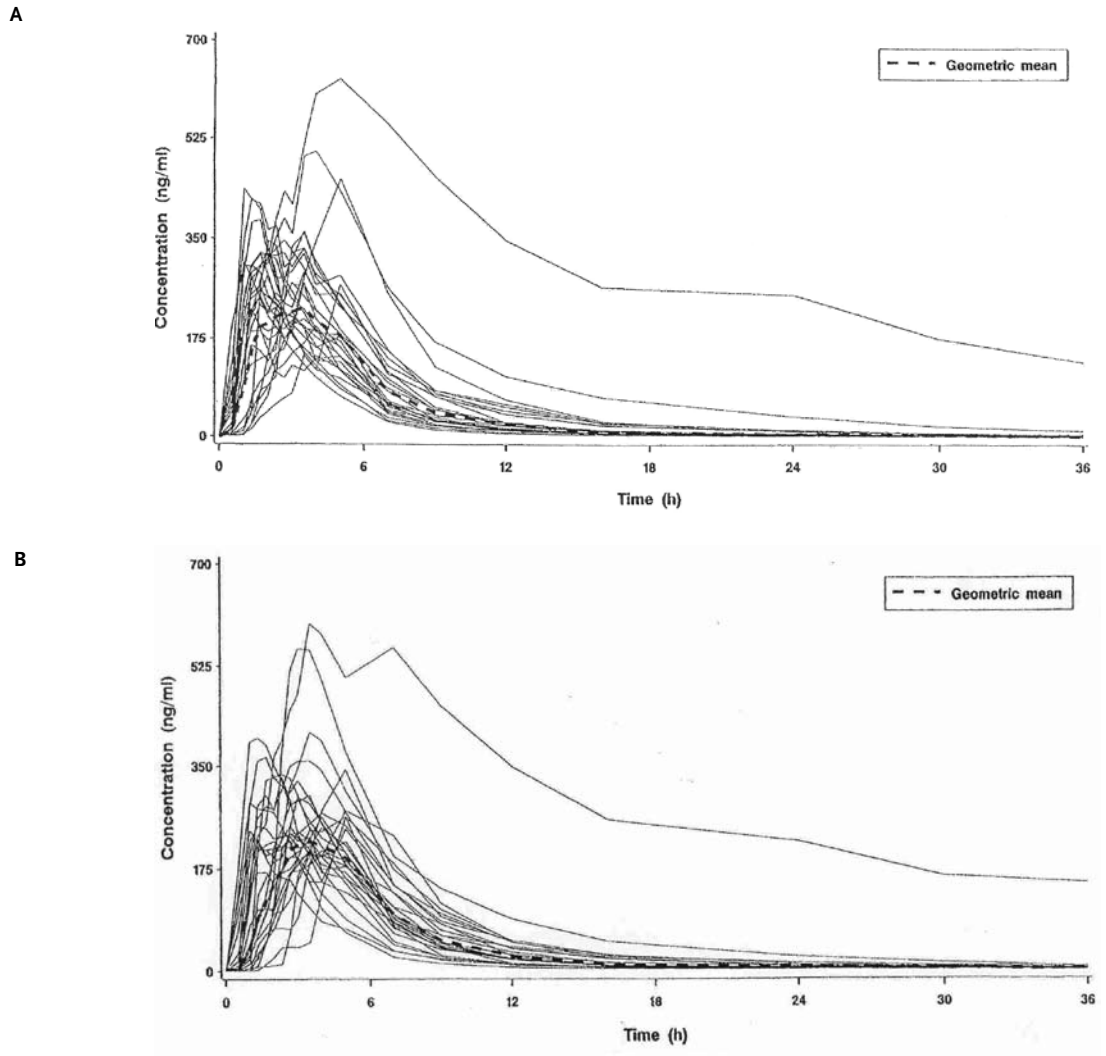
CONCERNS ABOUT GENERICS IN DAILY PRACTICE

Some concerns about the use of generics in daily practice are frequently expressed in the literature[1,3,6,7,16] and received by the CBG. The CBG is aware of additional circumstances which may unfortunately affect overall acceptance of generic substitution. Some questions that are posed frequently are dealt here.

Why is it sufficient for a systemically acting generic product to demonstrate bioequivalence with the branded medicine in healthy volunteers instead of demonstrating therapeutic equivalence in patients? The rationale for this is that there is always a relationship between the concentration profile of the active substance in plasma or blood over time and the efficacy and safety of the substance, although this relationship may be indirect. Consequently, if the active substance has a similar plasma concentration time course this will result in the same concentration at the site of action and is thus expected to result in an essentially similar efficacy and safety.

Does the outcome of a bioequivalence study in healthy volunteers also apply for the target patient population? Yes, with the bioequivalence study similar absorption into the systemic circulation of the active substance is demonstrated for the branded and generic products. This absorption from the intestine into the systemic circulation is the critical part, in which a difference in e.g. excipients between the branded and generic medicine may become apparent, and may thus have clinical consequences. After absorption, only the active substance, which is identical in the branded and generic medicine, will be present in the systemic circulation. Due to the active substance being identical and being present at the same levels, other intrinsic factors caused by illness e.g. local intestinal factors, renal or hepatic impairment, will have the same effect on the branded and generic medicine. That this principle works can be demonstrated by the effect of poor metabolisers in the bioequivalence study population. *Figure 2* is a typical example of such an event. From this figure it is clear that subject X has a much higher systemic exposure compared with the mean values of the study population. This high exposure was caused by the poor metabolising phenotype of this subject, leading to reduced metabolism and elimination, and thus to persistent high plasma levels of the active substance. It is, however, crucial to acknowledge that the higher exposure in this subject occurred for both the generic and the branded medicine (compare upper and lower *figures 2A* and *B*). From a clinical perspective it is clear that this poor metaboliser phenotype may well require a lower dose in order to avoid adverse events, but it is important to realise that this adjusted dose will be the same for the branded and the generic medicine. Therefore, although the absolute plasma levels deviate markedly and significantly

Figure 2. *Example of individual plasma concentration time course curves for the generic and branded medicine in a cross-over bioequivalence study*



from the mean exposure in the whole population, the AUC and Cmax generic/innovator ratios for this subject do not differ from the mean ratio of the population and hence the conclusion of bioequivalence is not affected. The same will happen for e.g., renally or hepatically impaired patients, or with any physiological differences between healthy volunteers and patients: the consequences will be the same for the generic and branded medicine. Bearing this principle in mind, in a crossover study design the subject is its own control and this means that formulation effects (generic *vs* branded medicine) can be evaluated without interference from such intrinsic factors affecting the bioavailability of the active substance. Therefore, the results obtained in healthy volunteer bioequivalence studies will be fully valid for the real-life patient population.

Are cheaper generics of lower quality? Cheaper medicines are sometimes interpreted as being of lower quality. However, this is not the case, the quality of the generic should meet exactly the same requirements as for the branded medicine. Moreover, pharmaceutical quality characteristics have sometimes improved considerably since the launching of the branded product. Pricing differences are possibly caused by the fact that at the time of registration of a generic, the efficacy and safety of the active substance are considered well established and there is no need for repeating the expensive (pre)clinical programme which was conducted for the branded medicine.

What about the name, colour and form? An issue which is relevant for acceptance of generic substitution by the public is the name, colour and form of the medicine.[18,19] As recognition by colour and form is an important visual check for the intake of medicines, such a difference for generic compared with branded products is a point of concern for an uncomplicated branded-generic substitution, especially

when many different products have to be taken daily. Moreover, the branded product has a 'fantasy' name, while the generic product is named after the active substance. The colour and form of the medicinal product as such is not part of the assessment of generics. As long as bioequivalence has been demonstrated, form and colour may be different from the branded product. The importance of colour and form for the public acceptance of a product can be illustrated with Losec (omeprazole): shortly after the introduction of the new branded tablets, Losec MUPS, as replacement for the original branded Losec capsules, many complaints on differences in efficacy were received at LAREB, the Pharmacovigilance Centre of the Netherlands.[20] Both branded products are from the same company and Losec MUPS was registered after bioequivalence and pharmacodynamic studies demonstrated equivalence with Losec capsules. This example indeed shows that the form and shape may be critical in the perception of being different. In order to deal with this issue, both prescriber and pharmacist can be of assistance by explicitly explaining that differences in name, colour and form of generic medicines do not affect the efficacy and safety of the medicine, as compared with the branded medicine.

What about generic vs therapeutic substitution? Another issue complicating acceptance of generic substitution in practice is that generic and therapeutic substitution are often confused and considered to be the same.[11] It is important to realise the difference between generic and therapeutic substitution: generic substitution means replacing the branded medicine by a bioequivalent generic containing the identical active substance, whereas therapeutic substitution means replacement by another registered product with another active substance from the same therapeutic class, for example substitution of omeprazole by pantoprazole. Since the pharmacokinetics and pharmacodynamics, and thus the benefit-risk ratio, of these different active substances may be different in a certain individual, there is no guarantee that therapeutic substitution will be harmless.

CONCLUSION

The CBG evaluates an application for registration of a generic medicine according to strict European Guidelines.[12-15] The CBG is of the opinion that when equal quality as well as equal exposure, by means of appropriate bioequivalence studies, has been demonstrated, the positive benefit-risk balance of the branded medicine also applies for the generic medicine. Consequently, the branded medicine can be safely exchanged with the generic product. If in an exceptional case an exchange between the generic medicine and the branded product is not possible, this is explicitly mentioned in the product's summary of product characteristics (SPC). Nevertheless, for an uncomplicated branded-generic substitution the above-mentioned concerns about the acceptance of generics in daily practice should be taken into account. It is clear that adequate communication to the patient, by prescriber, pharmacist and patient organisations, is essential for optimal generic substitution.

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ORIGINAL ARTICLE

A critical appraisal of indications for endoscopic placement of nasojejunal feeding tubes

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ABSTRACT

Background: Postpyloric feeding is indicated whenever nutritional intake is compromised because of impaired gastric emptying. Although guidelines concerning this feeding modality are available it remains unclear whether these are applied in clinical practice. We therefore evaluated the indications provided by applicants for endoscopic placement of nasojejunal feeding tubes at our centre.

Methods: A prospective study was conducted in patients who were referred for endoscopic nasojejunal-feeding tube placement in a 950-bed Dutch university hospital. State-of-the-art criteria for nasojejunal tube placement comprised severe gastro-oesophageal reflux, gastroparesis leading to aspiration, gastric stasis not responding to prokinetics, gastroduodenal obstruction or proximal enteric fistulae. The study endpoint was met if the feeding tube was no longer needed or had to be replaced, or if the patient was discharged from the hospital or died.

Results: During a four-month observation period, 131 patients were enrolled, of whom 57% came from intensive care units. Tube placement only met at least one of the mentioned criteria in the hospital protocol in 59% of all cases, while in intensive care patients a lower proportion was observed (50%, p<0.05). In the latter group, in 35% of all cases no increased gastric residues had been measured at all.

Conclusion: Although directives are at hand that provide clear indications for endoscopic placement of nasojejunal feeding tubes, our data show that these guidelines are frequently not followed in clinical practice. These findings suggest that supervised implementation of established guidelines might reduce the strain on both patients and the hospital's resources.

KEYWORDS

Artificial nutrition, endoscopy, feeding tube, intensive care, postpyloric feeding

INTRODUCTION

Postpyloric feeding is indicated when the digestive tract functions normally, but patients cannot meet their nutritional or fluid requirements due to a passage problem at the gastric level. This situation is most frequently encountered in the (early) postoperative setting.[1-7]

In general, there is consensus on the indications to initiate artificial nutrition, be it by the enteral or by the parenteral route.[1-12] Especially the European Society for Parenteral and Enteral Nutrition, the American Society for Parenteral and Enteral Nutrition, the American Gastroenterological Association and the British Society for Gastroenterologists have provided comprehensive guidelines on enteral and parenteral nutrition that represent the current state of the art.[7,8,10-12]

Several studies have compared gastric and postpyloric feeding with regard to indications and complications.[1-12] However, none of these focused on endoscopically placed nasojejunal feeding tubes (ENFTs). Although a few studies[13-22] have described tube survival rates, placement- and tube-associated complications, as well as the logistics regarding ENFTs, most of these investigations were too small to provide adequately assessable data from the statistical point of view.

This lack of information urged us to perform the present study. A small pilot survey in ten ICU patients who had ENFTs inserted because of supposedly impaired gastric emptying revealed only one patient with significant gastric retention according to our local protocol (>100 ml residue

twice within four hours). The reason for the discrepancies in the registration of gastric residues remained unclear and provided another indication for the present investigation. Here, we critically evaluated relevant issues concerning ENFT placement, with special emphasis on such critical issues as the correctness of the indications for tube placement, placement success and complications. For practical purposes, radiographically inserted nasojejunal feeding tubes were not included in this evaluation due to significant logistic differences between the endoscopic and radiological procedures.

MATERIALS AND METHODS

Study population

In total 131 consecutive patients who were referred for ENFT placement were enrolled in the study protocol. The local Committee on Research Involving Human Subjects approved the study. Because this work concerns a strictly observational study, informed consent was not mandatory. Adult patients (≥16 years) in whom endoscopical placement of an ENFT was requested were eligible for enrolment.
The study was conducted at the Radboud University Nijmegen Medical Centre in Nijmegen, the Netherlands, a university hospital where approximately 300 nasojejunal feeding tubes are inserted on an annual basis, 220 by means of endoscopy and 80 via radiological procedures.

Procedure

All requested ENFTs were made by means of an application form or by phone. The mobile endoscopy team inserted ENFTs on the ICU wards. All the other ENFTs were inserted on the Endoscopy ward. Following cannulation of the horizontal part of the duodenum, a Vygon Charriere 10 polyurethane feeding tube was inserted under direct vision through the biopsy channel and passed for at least 50 cm beyond the pylorus. All procedures were performed by gastroenterologists and fellows (94) or by a nurse practitioner (10).

State-of-the-art criteria

The state-of-the-art criteria for ENFT placement, according to various sources[1-7,10,14,15] are:

I. Proven severe gastro-oesophageal reflux, atonic stomach or gastroparesis leading to aspiration.
II. Delayed gastric emptying with residues >100 ml twice within four hours and not responding to propulsion improving measures.
III. Intolerance of oral feeding due to gastroduodenal inflammation, postprandial pain or passage disorder due to swelling or outside pressure onto the duodenum (pancreatitis or tumour).
IV. Proximal (duodenum and first part jejunum) enteric fistula.

Data

The study endpoint was met whenever the presence of an ENFT was no longer indicated, the ENFT had to be replaced, whenever the study period exceeded the observation period of four months, or if the patient was discharged from the hospital or died. All relevant data concerning indications and placement of the ENFT, hospital stay, complications and length of survival of the ENFT were recorded from the patients' medical files.

Statistical analyses

The primary endpoint of the study was the percentage of ENFTs that were correctly placed according to the state-of-the-art criteria. Given the lack of available data, and based on expert opinions, we assumed with an accuracy of 10% that about 60% of the requests for an ENFT would fulfil these criteria. Based on power analysis, an inclusion of 102 ENFTs was thus expected to permit adequate statistical analysis.
Descriptive statistics and comparisons of categorical variables between groups were evaluated using the Statistical Program for Social Sciences (SPSS) version 12.1 (SPSS Corporation, Chicago, Il, USA). Tube survival was assessed by means of Kaplan-Meier's analysis and log-rank testing.

RESULTS

Between February and June 2005, 131 adult patients who completed the study were enrolled, with a male-female ratio of 84:47 and a mean age of 60 years (range 17-87, SD = 14.9).
Outpatients (n=13) and patients with an observation period of less then one week (n=7) were excluded from the ENFT survival analysis. Most patients suffered from gastroenterological (41%) and cardiac (24%) problems. Overall, 57% of all patients had been admitted to the intensive care unit (ICU) at the moment the ENFT was requested.

State-of-the-art criteria

In 59% of all patients ENFT placement was found to fulfil one of the state-of-the-art criteria (*figure 1*). At ICUs this proportion was significantly lower (50%, p=0.01). Of note, in ICU patients, in 35% of all cases (n=74) no valid indication for ENFT placement was present since increased gastric residues had not been measured.

Withdrawn requests for ENFTs placement

Of the initially requested ENFTs, 27% originating from the ICUs (n=74) and 5% from other wards (n=57) were cancelled before actual placement (*tables 1* and *2*). A significantly higher number of withdrawals were observed for ICU requests (p≤0.001).

Figure 1. *Numbers of requested ENFTs that did or did not fulfil state-of-the-art criteria (I-IV)*

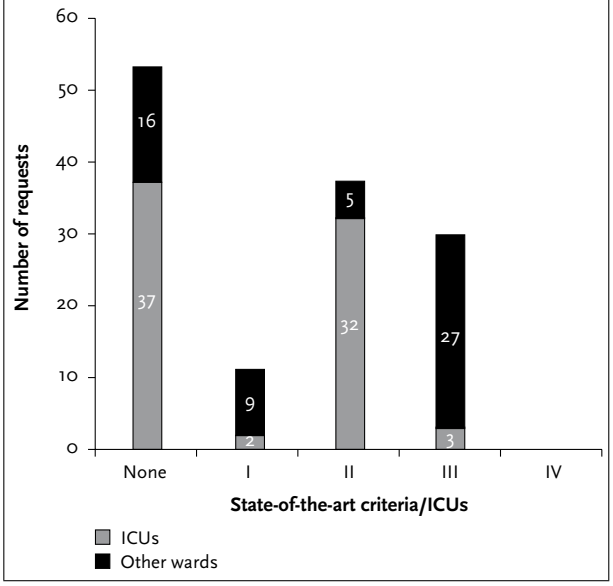

Table 1. *Details on ENFT placements in relation to state-of-the-art criteria*

ENFTs	Fulfilled criteria	Did not fulfil criteria	Total
Actual placement	75	28	103
Withdrawn placement	2	25	27
Failed placement	1	0	1
Total	*78*	*53*	*131*

Table 2. *Departments requesting ENFTs*

Department	Number	% of total
ICU Cardiothoracic	30	23
ICU Neurology/trauma	19	14
ICU General	25	19
Gastroenterology	18	13
Endoscopy centre	11	8
Surgery	8	6
Haematology	8	6
Internal medicine	4	3
Cardiology	2	2
Nephrology	2	2
Medium care (surgery)	1	1
Oncology	1	1
Ear, nose and throat	1	1
Radiotherapy	1	1
Total	*131*	*100*

ICU = intensive care unit. Underlying diseases comprised gastrointestinal (41%), heart (24%), trauma (10%) and neurological disorders (9%). Gastrointestinal disorders were mainly (47%) acute and chronic pancreatitis.

Cancellation in 89% of all cases (n=23) took place within 48 hours after the request. Except for one ICU patient, all withdrawals were reported to be the consequence of recovered gastric motility. Remarkably, 21 out of these 23 were initially requested because of reported significant gastric retention volumes.

Accidental findings during ENFT placement

During all endoscopic procedures (n=104) only one significant finding was reported in the form of a suspected peri-papillary lesion in the duodenum for which an appropriate analysis was initiated. Biopsies taken during this procedure were consistent with a duodenal adenoma. Small mucosal erosions, most likely due to the presence of feeding tubes, were seen on a regular basis in the gastric corpus and antrum. None of these gave rise to significant bleeding or required endoscopic intervention during the study period.

Time interval between request and ENFT placement

Most (30%) of the ENFTs (n=103) were inserted on a Friday. Probably because of the upcoming weekend (no ENFT placements are planned on a regular basis during the weekends in our hospital) there was probably an increase in requests on this day. It proved that 51% of all requests were carried out the same day and 79% within 48 hours.

Procedure-related complications

During endoscopic ENFT placement (n=104) no significant complications occurred. One procedure was aborted due to excessive vomiting. This patient developed no clinical symptoms related to aspiration.

Complications and survival of ENFTs in the clinical setting

Of all clinically inserted ENFTs 26% became nonfunctional within the first week after placement (n=83). Overall, almost 29% of the clinically inserted ENFTs eventually no longer functioned due to dislocation (either iatrogenic, or related to vomiting or agitation) and about 4% due to tube clogging. No statistically different (p=0.1124) survival rates were observed for ENFTs from ICUs when compared with other wards.

DISCUSSION

The most striking finding in the present study is that in a large university institution in a very high proportion (41%) of patients, despite the presence of well-established guidelines, ENFTs are not inserted in accordance with these directives. On the ICUs this proportion seems to be even higher (50%). Although this is a single-centre

investigation, we have no indications why our facility would not be representative for other teaching centres in the Netherlands.

ENFTs that were inserted according to the guidelines (59%) mainly concerned ICU patients (approximately 25%) who fulfilled criterion II (delayed gastric emptying with residues >100 ml twice within four hours and not responding to propulsion improving measures). For the other wards (surgical and internal medicine) criterion III (intolerance of oral feeding due to gastroduodenal inflammation, postprandial pain or passage disorder due to swelling or outside pressure onto the duodenum (pancreatitis or tumour)) was seen most frequently (21%). The indication for nearly all of these last requests was (chronic) pancreatitis.

The criteria for ENFT placement were clearly described by the physician and confirmed by checking the medical records immediately before actual insertion of the ENFT.

It remains unclear from our study why many (41%) ENFTs were not inserted according to the available guidelines. Our impression was that while these directives were known by heart by most physicians and nurses, they tend to rather act on their 'clinical instinct'. However, since only the state-of-the-art criteria are evidence based, it appears prudent that we should strongly adhere to their implementation.

The state-of-the-art criteria are based on expert reviews and guidelines. Although according to many surgeons peroperative nutritional support is an indication for the placement of a duodenal feeding tube in major bowel surgery[2-4,17,18,20] not one single ENFT was requested for this indication. This might be explained by the fact that in our hospital a (needle) jejunostomy is most frequently placed in this situation (on 37 occasions over the year 2006).

Another remarkable finding in this study was the high percentage (27%) of requested ENFTs by ICUs that were withdrawn within 48 hours. Although this in part probably reflects the clinical course of patients with recovered gastric emptying within this time frame, another explanation is that in a number of cases the judgement of gastric residues may have been incorrect.

The low number of coincidental findings during ENFT placements in this study has to be related to the fact that endoscopic visibility during the procedure is limited because tube feeding is only briefly interrupted before the procedure.

Some 26% of all ENFTs became non-functional within the first week after placement, mostly due to dislocation and clogging. This finding corroborates previous findings in the literature.[8,23]

We conclude that, at least in our institution, the guidelines that are at hand for ENFT placement are frequently not followed in clinical practice. Increased and persistent attention for practical nutrition-related issues in teaching programmes might well provide a solution in this regard.

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ORIGINAL ARTICLE

Preoperative chemoradiation with capecitabine in locally advanced rectal cancer

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ABSTRACT

Background: Preoperative radiation therapy in combination with 5-fluoracil (5-FU) improves local tumour control in locally advanced rectal cancer. The aim of our study was to evaluate the toxicity and efficacy of preoperative chemoradiation using the oral 5-FU prodrug capecitabine in locally advanced rectal cancer.

Methods: Sixty patients with locally advanced rectal cancer were treated with preoperative chemoradiation. Radiotherapy consisted of a total dose of 50 Gy delivered in 25 fractions to the pelvis. Chemotherapy was concurrently administered and consisted of oral capecitabine only on radiotherapy days. Surgery was performed six to ten weeks after completion of chemoradiation.

Results: The patient population consisted of 19 females and 41 males, with a median age of 61 years. All but two patients received the full dose of chemoradiation. No grade 3 or 4 haematological toxicities developed. Two patients (3%) developed grade 3 radiation dermatitis and one a grade 3 diarrhoea.

All patients underwent definitive surgery; 19 patients underwent an abdominal perineal resection (APR), 25 a low anterior resection (LAR) and 16 patients a Hartmann's procedure. One patient with a low anterior resection developed an anastomotic leakage (4%). Final pathology demonstrated eight patients (13%) with a complete pathological response. Primary tumour and nodal downstaging occurred in 67 and 84% of the patients, respectively. Two patients (3%) had an R1 resection, one after an APR and one after an LAR.

Conclusion: Preoperative chemoradiation with oral capecitabine is safe and well tolerated in locally advanced rectal cancer patients. This preoperative treatment has a considerable downstaging effect on the tumour and lymph nodes.

KEYWORDS

Capecitabine, chemoradiation, rectal cancer

INTRODUCTION

Preoperative radiotherapy with concurrent 5-fluorouracil (5-FU) based chemotherapy has received increased interest over the last decade in the treatment of locally advanced colorectal cancer. The addition of chemotherapy to radiation therapy has been demonstrated to be feasible, with an increase in pathological complete response rate and possibility of sphincter preservation. Preoperative chemoradiation therapy with 5-FU confers a significant benefit with respect to local control.[1,2] Continuous 5-FU infusion has been proven superior to bolus administration in terms of tumour response and is associated with a lower incidence of haematological and nonhaematological toxicity.[3,4] Disadvantages of continuous infusion are requirement of hospitalisation and potential complications resulting from central venous access.[5]

Capecitabine is a fluoropyrimidine carbamate rationally designed to generate 5-FU preferentially in tumour cells as the concentration of the key enzyme thymidine phosphorylase is higher in tumour cells compared with normal tissue. After irradiation thymidine phosphorylase is upregulated in tumour tissue resulting in a supra-additive affect of capecitabine on radiotherapy.[6-8] Capecitabine is administered daily to mimic continuous infusion of 5-FU. A phase I study of preoperative radiotherapy with 50.4 Gy given in 28 fractions in five weeks combined with escalating doses of capecitabine was reported by Ngan *et al.*[9] For phase II studies, they recommended a capecitabine dose of 1800 mg/m^2/day. This overall dose is similar to that used when capecitabine is given as a single agent for metastatic disease either in the 42-day continuous regimen (825 mg/m^2 twice daily) or in the intermittent schedule (1250 mg/m^2 twice daily for two weeks, one every three weeks).[10,11] Dunst *et al.* also conducted a phase I study and recommended 825 mg/m^2 capecitabine twice a day for phase II evaluation.[12] Three phase II studies have been initiated to evaluate the tolerance and efficacy of chemoradiation with capecitabine. In these studies different regimes of capecitabine were used and in some studies leucovorin was added.[13-16]

We initiated a phase II study to evaluate the efficacy and toxicity of preoperative chemoradiation with capecitabine in large T3/T4 rectal tumours or in tumours with local lymph node metastasis. In this study capecitabine was only administered on radiotherapy days.

MATERIALS AND METHODS

All patients treated in this study were evaluated including a complete history and physical examination, colonoscopy, tumour biopsy, abdominal ultrasound, computed tomography (CT) scan of the abdomen and pelvis and magnetic resonance imaging (MRI) of the pelvis, a chest X-ray and/or chest CT scan. All CT and MRI images of the patients were discussed in our multidisciplinary meeting which includes a colorectal surgeon, gynaecologist, urologist, radiotherapist, radiologist and medical oncologist. Complete laboratory tests included a full blood count with differential, serum chemistries including electrolytes, liver function tests, creatinine, and carcinoembryonic antigen.

Inclusion criteria

All patients had a histologically proven adenocarcinoma of the rectum. This was defined as any tumour within 15 cm of the anal verge or a tumour located distal from the line between the promontory and symphysis on sagittal MRI. The location of the tumour was measured from the anal verge using colonoscopy.

Patients with large T3 or T4, Nx or any T3, N1-2 rectal adenocarcinoma were eligible for the study. Large T3 tumours were defined on pelvic MRI as tumours with narrow margins (<2 mm) to the circumferential rectal fascia. Mesorectal and obturator lymph nodes were considered positive on pelvic MRI if a node was larger than 8 mm or multiple nodes larger than 3 mm. All patients needed to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and be aged between 18 and 80 years. Patients also had to have adequate liver, renal and bone marrow function as follows: bilirubin <30 μmol/l, aspartate aminotransferase and alanine aminotransferase less than five times the upper level of normal (ULN), creatinine <1.5 x ULN, leucocytes >3.5 x 10^9/l, and platelets 100 x 10^9/l. Patients of child-bearing age were required to practice approved methods of birth control.

Exclusion criteria

Patients with severe comorbidity such as cardiomyopathy or other cardiovascular disease were excluded. Patients with known risk of adverse reaction to fluoropyrimidines were excluded, as well as patients who were participating in other trials or receiving any investigational drugs.

TRIAL DESIGN AND ENDPOINTS

This was a single-armed, multicentre phase II study of preoperative radiotherapy with concurrent capecitabine for locally advanced rectal cancer. Primary endpoints were toxicity, grade of tumour downstaging and pathological complete response. Secondary endpoints were rate of sphincter preservation and postoperative complications. Primary endpoints were haematological and nonhaematological toxicity. Toxicity was scored with Radiation Therapy Oncology Group criteria and the National Cancer Institute Common Toxicity Criteria version 3.0. Secondary endpoints were complete pathological response, pathological downstaging and sphincter preservation. Our definition of downstaging and complete response was based on the comparison of the clinical tumour node metastasis (TNM) and the pathological TNM stage. Pathological complete response was defined as no tumour cells in the pathological specimen, but only a fibrotic mass.

Chemotherapy

Capecitabine was administered orally at a dose of 825 mg/m^2 twice a day only on radiotherapy days. The first daily dose was given two hours before radiotherapy and the second dose twelve hours later. Dose modifications were applied if the patient experienced any grade 3 or 4 haematological toxicity or any grade 3 nonhaematological toxicity, such as hand-foot syndrome, except for alopecia. Chemotherapy was restarted at a 75% dose if toxicity levels resolved to grade 1 or less. If toxicity was clearly related to radiotherapy, for example radiation dermatitis, local therapy was administered and capecitabine was not stopped.

Radiotherapy

All patients were treated with preoperative radiotherapy and received a dose of 50 Gy delivered in 25 fractions of 2.0 Gy. Radiotherapy was administered by a three-field technique, using one posterior and two lateral portals, a four-field box or with five fields using intensity modulated radiotherapy. The lateral pelvic borders were defined as 1.5 cm lateral of the bony pelvis, the cranial border was the promontory, and the caudal border was below the foramina obturatoria to 2 cm under the anus, depending on tumour position. Patients were evaluated four times during the course of chemoradiation to assess acute toxicity and compliance with the oral capecitabine. Blood tests were taken each time and consisted of full blood count, platelets, leucocytes and neutrophils.

Surgery

Surgery was performed six to ten weeks after completing chemoradiation. Patients were reassessed for resectability by pelvis CT scanning or MRI of the pelvis. Total mesorectal excision technique was performed in all patients, and extended multivisceral resections were performed in clinically T4 patients. Intraoperative

radiotherapy was administered in those patients in whom the circumferential margins were considered at risk.

RESULTS

A total of 60 patients were included between July 2005 and November 2006. The median age was 61 years (range 32 to 82 years) and the majority of patients had T3N1-N2 (48%) stage of disease. Other patient characteristics are shown in *table 1*. Median distance to the anal verge was 5 cm (range 0 to 20 cm). Most of the tumours were located in the lower parts of the rectum, with only a minority (13%) above 10 cm (*table 2*). In one patient the tumour was measured at 20 cm from the anal verge, but after discussing this case in our multidisciplinary team, we considered the bulk of the tumour to be in the upper part of the rectum, in close relation to the bladder. In this case downsizing of the tumour was aimed for and chemoradiation was proposed. All patients underwent surgery and were evaluated for pathological response and downstaging.

Toxicity

Toxicity was moderate and is summarised in *table 3*. Hand-foot syndrome did not occur in any of the patients.

Table 1. *Baseline patient characteristics*

Category	Number (%)
Gender:	
• Male	41 (68)
• Female	19 (32)
Performance status (ECOG):	
• 0	40 (67)
• 1	20 (33)
Histological differentiation:	
• Moderate	44 (73)
• Poor	3 (5)
• Unknown	13 (22)
Clinical tumour stage:	
• T3NO	3 (5)
• T3N+	29 (48)
• T4NO	12 (20)
• T4N+	16 (27)

ECOG = Eastern cooperative oncology group.

Table 2. *Tumour location and surgical treatment*

Tumour location	Number	APR (%)	LAR (%)	Hartmann (%)
>10 cm	8	1 (12)	4 (50)	3 (38)
5-10 cm	20	2 (10)	13 (65)	5 (25)
<5 cm	32	16 (50)	8 (25)	8 (25)
All tumours	60	19 (32)	25 (42)	16 (27)

APR = abdominal perineal resection; LAR = low anterior resection.

No haematological grade 3 or 4 toxicities occurred. Haematological toxicity was mild with grade 2 anaemia, leucocytopenia and neutropenia in 7, 12 and 3% of the patients, respectively. The only grade 3 nonhaematological toxicity was radiation dermatitis (3%) and diarrhoea (2%). Chemoradiation was not stopped in two patients who developed grade 3 radiation dermatitis. This occurred at the end of therapy and was managed by applying local therapy. All but two patients received the full dose of chemoradiation. A 56-year-old male reported severe chest pain while taking capecitabine, which was absent in the weekend. There was no history of cardiac disease. Capecitabine was stopped and radiation continued. A second patient was a 49-year-old female who experienced grade 3 diarrhoea which required intravenous fluid replacement. Capecitabine was stopped and not restarted at patient's request; radiotherapy was continued.

Response

Surgery was performed in ten different hospitals and all patients underwent definitive surgery. In 19 patients an abdominal perineal resection (APR) was performed, in 16 a Hartmann's resection and in 25 a low anterior resection (LAR). Of the patients with T4 tumours, 18 underwent a multivisceral resection: five posterior exenterations, three total exenterations, three vagina resections, two partial bladder resections, three seminal vesicle resections and two partial prostate resections.

A complete pathological response was achieved in eight patients (13%) (*table 4*). Overall tumour and nodal downstaging occurred in 51 patients (85%). Tumour downstaging was seen in 40 patients (67%) and overall nodal downstaging in 38 patients (84%). Tumour progression during chemoradiation was not observed. Final pathology demonstrated To in eight patients (13%), T1 in six patients (10%), T2 in 14 patients (23%), T3 in 27 patients (45%) and T4 in five patients (8%).

Table 3. *Haematological and nonhaematological toxicity*

Toxicity	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Haemoglobin	-	4 (7)	-	-
Platelets	15 (25)	-	-	-
Leucocytes (total WBC)	22 (37)	7 (12)	-	-
Neutrophils	-	2 (3)	-	-
Hand-foot skin reaction	1 (2)	-	-	-
Radiation dermatitis	14 (23)	11 (18)	2 (3)	-
Nausea	9 (15)	1 (2)	-	-
Vomiting	-	-	-	-
Lower gastrointestinal (diarrhoea)	11 (18)	1 (2)	1 (2)	-
Genito-urinary	13 (2%)	-	-	-

WBC = white blood count.

Of the 32 patients with initial tumour location less then 5 cm from the anal verge, 16 underwent an abdominal perineal resection and eight (25%) sphincter preservation by performing a low anterior resection. The majority of patients with the initial tumour location more than 5 cm from the anal verge underwent an LAR; only three patients underwent an APR, and eight a Hartmann's resection. In two patients (3%) an R1 resection was performed; one male patient with a tumour located at 3 cm from the anal verge underwent an APR and another male patient with a tumour located at 8 cm from the anal verge underwent a low anterior resection. No R2 resections were performed. Anastomotic leakage in the low anterior group occurred in one patient (4%).

DISCUSSION

Patients with locally advanced rectum carcinoma should preferably receive some form of neoadjuvant treatment to downstage the tumour and enable a potentially curative resection. 5-FU-based chemoradiation is currently a well-accepted approach in the management of locally advanced rectum carcinoma. We conducted the present study to evaluate toxicity and efficacy of preoperative chemoradiation using oral 5-FU (capecitabine) in locally advanced rectal cancer. This should potentially lead to improved local tumour control and improved chance of sphincter preservation. We demonstrated that preoperative chemoradiation therapy with capecitabine is feasible with acceptable overall grade 3 toxicity of 5% and a 13% complete response rate.

All patients treated in this study completed radiotherapy and all but two completed chemotherapy. The incidence of acute toxicity in the present study was slightly lower than other phase II trials using capecitabine.[13-15] *Table 5* demonstrates the results from the present study and three previously published studies. These differences can possibly be explained by the regime of capecitabine that was administered. Considering the radiation sensitising dose and effect of capecitabine in this set-up,[17] we designed the study to give capecitabine only on radiotherapy days. Because of the two-day resting period every five days, toxicity might therefore be lower than in the other series where capecitabine was administered twice daily, seven days a week. Kim *et al.* used a regime consisting of two cycles of 14 days followed by a resting period of seven days and also added leucovorin to their regime. It is noteworthy that one of the patients in the present study had severe chest pain with no history of any myocardial disease. Cardiotoxicity is a well-known but rare adverse effect of capecitabine and has been reported in several case reports.[18-20]

In a previous study of locally advanced rectal carcinoma in our centre, radiotherapy was used at a similar dose (25 x 2 Gy), but without capecitabine demonstrating a complete pathological response rate of only 2%.[21] In the present study a large group of patients (47%) who had a clinical T4 tumour were treated and despite this a complete pathological response of 13% and a total tumour downstaging of 67% were observed. Complete pathological response rates were slightly higher in the other reported phase II trials, but these differences can be explained by the fact that other phase II studies had considerably less patients with clinical T4 tumours. In the subgroup of patients with T4 staged tumours, one patient (4%) had a complete response and 24 of 28 patients (84%) had a total tumour downstaging. Of the 45 patients with clinical positive nodal status only eight (18%) had pathological nodal involvement. Unfortunately, there is a potential bias in all studies that report on rectal cancer downstaging. The real downstaging effect of the chemoradiation treatment can not be accurately measured, since clinical nodal staging is based on diagnostic imaging and is not pathologically proven. However, we used strict criteria for node positivity on pelvic MRI and all patients were discussed in a multidisciplinary team.

All patients in our study had definitive surgery after preoperative therapy. Multivisceral resection, which was previously proven to enable good local control and acceptable survival, was performed in 18 patients.[22] The considerable downstaging effect of the addition of capecitabine to a long series of radiation may increase the chance of sphincter preservation and decrease the need for multivisceral resection. Bujko *et al.* demonstrated no significant increase in sphincter preservation after 5-FU based chemoradiation therapy, despite an increased clinical response rate.[23] Other studies demonstrated a significant correlation between

Table 4. *Distribution of clinical tumour stage compared with pathological tumour stage*

Clinical: tumour and node	pT0N0	pT1N0	pT2N0	pT2N1	pT3N0	pT3N1	pT3N2	pT4N0	pT4N2	Total (%)
cT3N0	1	1	1	-	-	-	-	-	-	3 (5)
cT3N1	3	-	4	-	8	3	-	-	-	18 (30)
cT3N2	3	3	1	-	2	-	2	-	-	11 (18)
cT4N0	1	2	3	1	2	-	-	3	-	12 (20)
cT4N1	-	-	4	-	9	-	-	1	-	14 (23)
cT4N2	-	-	-	-	-	-	1	-	1	2 (3)
Total (%)	*8 (13)*	*6 (10)*	*13 (22)*	*1 (2)*	*21 (35)*	*3 (5)*	*3 (5)*	*4 (7)*	*1 (2)*	*60*

Table 5. *Comparison of trials of preoperative chemoradiation therapy in locally advanced rectal cancer*

Study	Patients (n)	Treatment	Down-staging rate (%)	Response (%)	Ro/R1 resec-tions	Toxicity	T3/T4	Sphincter preserva-tion
De Paoli[15]	53	Pelvic RT (45 Gy in 25 fractions, 5 days/week)+ boost to tumour (5.4 Gy in 3 fractions) +c (825 mg/m² bid) 7-days/week	57%	pCR 24%,	48/3	Grade 3 6 patients (11%) = leucopenia 4% + hand-foot syndrome 4%	46/7	59%
Kim[16]	38	Pelvic RT (45 Gy in 25 fractions, 5 days/week)+ boost to tumour (5.4 Gy in 3 fractions) + c (825 mg/m² bid) + LV (20 mg/m²/day) days 1-14 week, 2 cycles of 14 days	63%	pCR 31%,	NR	Grade 3 hand-foot syndrome (7%), fatigue (4%), diarrhoea (4%) and radiation dermatitis(2%)	33/4	72%
Krish-nan[13]	54	Pelvic RT (45 Gy in 25 fractions, 5 days/week)+ concomitant boost to tumour (7.5 Gy in 5 fractions) + c (825 mg/m² bid) continuous 35 days.	51%	pCR 18%	51/0	Grade 4 diarrhoea 2%, Grade 3 lymphopenia 70%, anaemia and neutropenia 2%, radiation dermatitis 9%, proctitis 4%, fatigue 2%, diarrhoea 2%	52/2	67%
Present	60	Pelvic RT (50 Gy in 25 fractions, 5 days/week) + c (825 mg/m² 5 days/week)	67%	pCR 13%	58/2	Grade 3 2% diarrhoea, 3% radiation dermatitis	32/28	50%

RT = radiotherapy; pCR = pathological complete response; LV = leucovorin; bid = twice daily.

chemoradiation and sphincter preservation.[24] In the present study only eight patients (25%) with a low-lying tumour (≤5 cm from anal verge) underwent sphincter preserving surgery. Therefore, conclusions regarding the benefit of chemoradiation on sphincter saving surgery can not be made based on the experience in this study.

The incidence of circumferential margin involvement in patients with locally advanced rectal cancer is higher compared with rectal cancers were the tumour is confined to the mesorectum. Especially in APR patients circumferential resection margins are more often involved compared with patients who undergo an LAR.[25] In the present study, two patients (3%) had an R1 resection; one after an APR and one after an LAR. The downstaging effect of chemoradiation might decrease the risk of circumferential involvement, but surgical technique is also important. For instance, in patients who underwent an APR resection, wide perineal resection seems to decrease the risk of involved margins and improve outcome.[26] Further improvement of outcome can be expected using new neoadjuvant chemoradiation protocols including chemotherapeutic drugs such as oxaliplatin or irinotecan.[27,28] Willet *et al.* have reported promising results using a vascular endothelial growth factor (VEGF) specific antibody (Bevacizumab) in combination with 5-FU-based radiotherapy.[29] This has lead to the conduction of a multicentre feasibility trial (RAX) in the Netherlands for which patients are currently being included.

CONCLUSION

Preoperative chemoradiation with oral capecitabine is safe and well tolerated in locally advanced rectal cancer patients. In addition, this preoperative treatment has a considerable downstaging effect on the tumour and lymph nodes resulting in few R1/R2 resections in large T3 and T4 rectal carcinoma. Capecitabine is used as a radiation sensitiser and there seems to be no need to administer it on nonradiotherapy days. By doing so it might minimise toxicity without influencing response.

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CASE REPORT

Tuberculous peritonitis during infliximab therapy

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ABSTRACT

Reactivation of tuberculosis is a severe side effect of anti-TNF treatment. Especially extrapulmonary forms of tuberculosis may occur, which are difficult to diagnose. The diagnosis may be obtained by a thorough search for *Mycobacterium tuberculosis*. We describe two patients who developed tuberculous peritonitis after infliximab therapy that was prescribed for treatment of rheumatoid arthritis. These cases illustrate that tuberculous peritonitis has a nonspecific clinical manifestation and that *Mycobacteria* can be difficult to find in ascites fluid. For this reason, tuberculostatic therapy has to be started in case of clinical suspicion. Before starting infliximab therapy, the patient must be thoroughly screened for the presence of (latent) tuberculosis.

KEYWORDS

Infliximab, TNFα antagonist, tuberculous peritonitis

INTRODUCTION

Tumour necrosis factor-α (TNFα) is a proinflammatory cytokine that plays an important role in the pathogenesis of inflammatory diseases such as rheumatoid arthritis. Infliximab, an anti-TNF monoclonal antibody, improves symptoms and slows down articular erosions in patients with rheumatoid arthritis who are nonresponsive to conventional therapy. Although TNFα antagonists have dramatically improved the outcome in chronic inflammatory diseases, interference with the host defence mechanism is a major concern. TNFα increases the ability of macrophages to phagocytose intracellular micro-organisms and is required for the formation of granulomas.[1] Patients using infliximab are prone to intracellular bacterial infections and especially to reactivation of latent tuberculosis. We describe two patients with a rare extrapulmonary form of tuberculosis as reactivation of a latent infection after infliximab therapy.

CASE REPORTS

Case report 1

A 68-year-old female, born in Indonesia and living in the Netherlands for 50 years, had been treated for rheumatoid factor positive rheumatoid arthritis for 21 years. Different drugs had been prescribed to control the disease. In 2002, infliximab infusions were started with satisfactory results (infusion on week 0-2-6). After the start of infliximab, purified protein derivative (PPD) test showed an induration of 3 cm, and the patient was treated with isoniazid for six months. Infliximab infusions were interrupted for one month and resumed at eight weekly intervals thereafter.

In 2006, the patient was hospitalised because of progressive pain in the lower part of the abdomen, periods of fever and weight loss of 7 kg in three weeks. No micro-organism was found on multiple blood cultures. Ultrasounds revealed ascites and a swollen omentum. Ascites fluid contained no malignant cells, and both auramine staining and polymerase reaction chain (PCR) on *Mycobacterium tuberculosis* were negative. Despite antibiotic therapy (piperacilline/tazobactam), the fever persisted and her condition aggravated. Using diagnostic laparoscopy, a biopsy of the peritoneum was performed; histology showed inflammation without evidence of granulomas or malignancy. The biopsy showed negative auramine staining and the PCR on *M. tuberculosis* was negative. The absence of other causal agents of peritonitis in a patient at risk for tuberculosis made us decide to start tuberculostatic therapy. After several weeks of therapy her clinical condition

ameliorated and the patient returned home after two months of hospitalisation. Three months later, culture of the peritoneum biopsy was positive for *M. tuberculosis*.

Case report 2

A 53-year-old female Vietnamese patient with rheumatoid arthritis was treated in 2003 with infliximab infusion because of active disease despite immunosuppression. The PPD skin test before the start of infliximab infusion was negative while the patient was taking corticosteroids and methotrexate. After three months of infliximab therapy the patient developed abdominal pain. Tuberculous peritonitis was suspected and the infliximab infusions were interrupted. The chest X-ray showed no signs of tuberculosis. After the start of tuberculostatic therapy (isoniazid, rifampicine and pyrazinamide), the diagnosis was confirmed by culturing *M. tuberculosis* from ascites fluid. The therapy was halted after three weeks because of hepatitis, which was likely to be treatment-induced. After normalisation of her liver enzymes, tuberculostatic therapy was restarted with ethambutol, levofloxacin and rifampicin. This time the liver enzymes remained within normal limits. During the reintroduction of her tuberculostatic therapy she developed an asymptomatic miliary tuberculosis on her chest X-ray. Seven months after the initial diagnosis of tuberculous peritonitis and still on tuberculostatic therapy, the patient noticed two tumours on the chest at 3 cm below the clavicles, each measuring about 3 x 4 cm. Fluid aspiration of the tumours revealed auramine-negative, PCR-positive tuberculosis material. Tuberculostatic therapy was halted after one year of treatment and so far she is doing well.

DISCUSSION

The TNFα antagonist infliximab is an effective drug for reducing inflammatory conditions in patients with rheumatic disorders (such as rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis and psoriatic arthritis) or Crohn's disease.[2] However, since the introduction of this agent in 2000, cases have been reported of tuberculosis associated with infliximab.[3] The interruption of TNFα activity decreases the cell-mediated immune response to *Mycobacterium tuberculosis*. During TNFα blockade, the immune system is not able to envelop the *Mycobacterium* into granulomas. As a consequence, infliximab use appears to be associated with a fivefold increased risk of tuberculosis, which is mainly related to reactivation of latent infection.[4] The frequency of tuberculosis in patients on infliximab therapy was much higher compared with other opportunistic infections such as listeriosis, histoplasmosis, aspergillosis and candidiasis.[5] In 2001, Keane *et al*. described reports of tuberculosis after infliximab therapy through the MedWatch spontaneous reporting system of the Food and Drug Administration (FDA's Adverse Event Reporting System (AERS)).[6] Among the 70 patients reported to have tuberculosis during or after infliximab therapy, the median interval from the start of infliximab to development of tuberculosis was 12 weeks (range 1-52). The number of cases with extrapulmonary tuberculosis exceeded those of pulmonary tuberculosis in patients on infliximab therapy. In the general population only 17.5% of all tuberculosis cases is extrapulmonary.[5] The data from the AERS showed that of the 70 cases of tuberculosis occurring during TNFα antagonism, 56% had extrapulmonary tuberculosis and a high percentage (24%) miliary tuberculosis (which has a high mortality rate).[7]

Many studies have followed since the question arose as to whether the increased risk of tuberculosis in patients is due to TNFα antagonists therapy. Increased tuberculosis incidence was confirmed in patients with rheumatoid arthritis,[8,9] although some say this is due to incomplete screening for tuberculosis.[10]

Extrapulmonary forms of tuberculosis are often difficult to diagnose. Because the patients in the described cases used infliximab, the diagnosis of tuberculous peritonitis was suspected. After several weeks to months, the diagnosis was confirmed by culture. Although we can never be sure, in our opinion the patients had a reactivation of latent tuberculosis because of their provenance from origins in areas with high tuberculosis incidence and no known recent tuberculosis contact.

Tuberculous peritonitis is an uncommon manifestation of tuberculosis. The underlying mechanism is thought to be haematogenous spread of bacilli from active pulmonary lesions or activation of latent foci of tuberculous infection of the peritoneum. Patients most frequently present abdominal swelling, anorexia and ascites. Fever, weight loss, abdominal pain, diarrhoea and abdominal tenderness commonly occur; however, the presentation can be aspecific. Routine laboratory tests generally demonstrate chronic inflammatory disease with mild anaemia and elevated sedimentation rate, white blood cell count is usually normal. Proof of tuberculosis is often difficult to find and may only be obtained if a specific search is carried out for *M. tuberculosis*. Because this is a slow-growing bacteria, the results of the culture can take several weeks to three months. In case of clinical suspicion, tuberculostatic therapy should not be delayed, as waiting for culture results may have fatal consequences. Clinician inexperience with tuberculosis is one of the reasons why patients in the Western world still die of the disease. *Table 1* presents the diagnostic tools in case of suspicion tuberculous peritonitis. Positive skin reaction to PPD helps make a diagnosis, although negative results are not informative in immunosuppressed patients (e.g. with rheumatoid arthritis). Candidates for infliximab therapy

Table 1. *Diagnostic tools in case of suspicion of tuberculous peritonitis*

Diagnostic strategy		**Possible results**	
Purified protein derivative test (Mantoux)		Negative in immunocompromised patients	False positive after BCG vaccination
Chest X-ray		Signs of old pulmonary disease and sometimes active disease	
Echo abdomen		Ascites, fixed membranes, septa, debris, thickened mesentery and lymphadenopathy	
CT abdomen		High density ascites and lymphadenopathy with low-density centre suggestive for necrosis	
Ascites fluid	Cytology	Straw coloured exudates with lymphocytic predominance	
	Ziehl-Neelsen, auramine		3% of the cases positive
	PCR	Negative result does not excludes tuberculosis	
	Culture (golden standard)	Result should not be awaited to start therapy	10-20% of the cases positive
Peritoneum biopsy	Histology	White caseating granulomas, peritoneal adhesions, multiple yellow white miliary nodules	85-90% caseating granulomas,
	Ziehl-Neelsen, auramine		75% of cases positive
	PCR	Negative result does not exclude tuberculosis	
	Culture (golden standard)	Result takes weeks to months	

are frequently on immunosuppressive therapy because of their underlying rheumatic or inflammatory bowel disease. Skin reaction is also of limited use after BCG vaccination. Chest X-ray may show signs of old pulmonary disease and sometimes active disease. Abdominal echography and CT may demonstrate abdominal lymphadenopathy and the presence of ascites. Unfortunately, *M. tuberculosis* in ascites fluid is found in only 3% of the patients.[11] Several series of patients showed that PCR of ascites fluid is successful in confirming the diagnosis.[12,13] However a negative result does not rule out tuberculous peritonitis.[14] Cultures of ascites fluid are positive in 10 to 20% of the patients with tuberculous peritonitis. Culture of a large volume of ascites fluid can increase the yield, but peritoneal biopsy is often needed to establish the diagnosis. Direct laparoscopic inspection and biopsy of the peritoneum reveal multiple, yellow-white 'miliary' nodules of the visceral and parietal peritoneum. The biopsies show acid-fast rods in 75% of the cases and caseating granulomas in 85 to 90%.[11] Moatter *et al.*[15] described that PCR assay on intestinal tissue can accelerate the diagnosis, especially when several primers are used. The exact positive predicted value of PCR in tuberculous peritonitis needs to be established. Although the result is awaited for weeks to months, positive culturing may confirm eventually the diagnosis.

Few cases of tuberculous peritonitis in patients on infliximab therapy have been described in literature.[16,17] It is very likely that many cases are left unreported.[18] The second database that demonstrated increased risk of tuberculosis among patients on infliximab for treatment of rheumatoid arthritis showed no patients with tuberculous peritonitis among 17 cases.[19] Because of the insidious presentation and the difficulty in finding acid-fast bacilli, tuberculous peritonitis is likely to remain undiscovered in patients on infliximab.

In sum, tuberculous peritonitis is an uncommon extrapulmonary expression of tuberculosis. Reactivation of latent tuberculosis is the most notorious side effect of infliximab. Before starting infliximab therapy the patient has to be thoroughly screened for the presence of (latent) tuberculosis. The guidelines of the Dutch Society of Rheumatology advise screening for latent or active tuberculosis in all patients before starting TNFα blockade. The patient should be questioned and examined for signs of tuberculosis. A chest X-ray and tuberculin skin test should be performed. If active tuberculosis is detected, it should be adequately treated before TNFα blockade is started. Latent tuberculosis should be treated with 9 to 12 months of isoniazid therapy.[20] Case 1 demonstrates that PPD skin testing was performed after the start of infliximab therapy. The TNFα inhibition had to be interrupted for the treatment of latent tuberculosis. The patient was treated with isoniazid for six months. Although we have no information on the most effective duration[4,21] of isoniazid therapy the guidelines advise treating for at least nine months.[20] In case 2 the PPD skin reaction was negative which illustrates the difficulty in diagnosing latent tuberculosis in immunocompromised patients.

The lack of a gold standard for latent tuberculosis makes the decision to start treatment difficult. Interferon-gamma release assays (IGRA) are now available alternatives to tuberculin skin tests.[22,23] In contrast to tuberculin skin tests, IGRA is usable in BCG-vaccinated patients because

it measures *in-vitro* T-cell responses to antigens of *M. tuberculosis*. This test has not yet been introduced in clinical practice because a negative result does not prove an absence of viable bacilli.

The infectious risk is not the same in different TNFα blockers. Tumour necrosis factor-α is a proinflammatory cytokine that is particularly produced by macrophages and T lymphocytes as a stimuli to micro-organisms. It is responsible for apoptosis and acts with interferon-γ (IFNγ) to generate cell mediated immune response to pathogens as *M. tuberculosis*. TNF is essential for granuloma formation and maintenance which are key components of host defence against intracellular pathogens. For this reason infliximab (partly human-mouse monoclonal antibody) and the fully human monoclonal antibody adalimumab, are also effective in treatment of granulomatous diseases as Crohn disease. Infliximab and adalimumab inhibit T-cell activation and IFNγ production *in vitro*. They neutralise membrane-bound TNFα in addition to the soluble fraction. The TNFα blocker etanercept decreases levels of circulating TNFα by binding soluble TNFα with its receptor domains. This difference makes it ineffective in granulomatous intestinal disease.[24] It might be argued that infliximab and adalimumab directly interfere with granuloma integrity and etanercept predominantly neutralises excessive inflammatory response.[25] This may explain the greater risk of reactivation of latent tuberculosis during the first three months of infliximab treatment compared with etanercept.[24,26,27]

To conclude, in rheumatoid arthritis and Crohn's disease the tuberculin skin reaction can be false-negative due to immunosuppressive states. Before starting TNFα blockers, patients should be adequately screened for (latent) tuberculosis. When patients are suspected of having tuberculosis it is of crucial importance to obtain material for the diagnosis and to start tuberculostatic drug therapy as early as possible. This holds especially true in patients at risk for tuberculosis, for example because of infliximab use.

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CASE REPORT

Measurement of leg blood pressure: the most straightforward way to the diagnosis

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ABSTRACT

Two adult patients with presumed primary hypertension are presented. In the first patient the diagnosis of coarctation of the aorta was straightforward while in the second patient there was a substantial delay in reaching the correct diagnosis.

A 32-year-old patient was analysed for hypertension in the outpatient clinic. At physical examination a systolic cardiac murmur was present and leg blood pressure was not measurable. Magnetic resonance imaging angiography showed a severe coarctation of the thoracic aorta with extensive distended collateral blood vessels. A second patient was a 31-year-old man referred with longstanding hypertension and an unsatisfactory blood pressure response to treatment. Previously, a diagnosis of primary hypertension was made. Renal computed tomography angiography excluded renal artery stenosis as a cause of hypertension but disclosed many distended collateral blood vessels in the musculus rectus abdominis and in the upper abdominal area. Leg blood pressure was measured and further analysis revealed a coarctation of the aorta.

Both patients illustrate and emphasise the importance of leg blood pressure measurement at a first analysis of adult hypertensive patients and should always be performed when hypertension is accompanied by murmurs or weak femoral pulsations.

KEYWORDS

Aortic coarctation, blood pressure determination, case reports

INTRODUCTION

Coarctation of the aorta is a rare cause of hypertension. It accounts for 5 to 7% of all congenital heart defects.[1] In most cases it is located immediately distal to the origin of the left subclavian artery at the site of the ductus arteriosus. Males are affected twice as often as females. Other cardiac malformations may be present and there is a prominent association with a bicuspid aortic valve in up to 80% of the patients.[2]

The exact prevalence of coarctation of the aorta in young and adult hypertensive patients is not exactly known. Since children with an isolated coarctation are usually asymptomatic except for hypertension, the diagnosis may be established later in life and can only be made if the femoral pulses are weak or if leg blood pressure is substantially lower than arm blood pressure. We present two adult hypertensive patients with a diagnosis of aortic coarctation. The first patient demonstrates that careful and complete physical examination will lead to a rapid diagnosis of the coarctation. The second patient demonstrates that the repeated omission of blood pressure measurement in the leg during physical examination will inevitably lead to a severely delayed diagnosis of coarctation of the aorta.

CASE REPORTS

Case report 1

The first patient was a 32-year-old male who presented at the outpatient clinic for analysis of untreated hypertension of approximately five-year duration. He was asymptomatic and had no other cardiovascular risk factors. In his family only his mother was known with hypertension. On physical examination, blood pressure was 162/92 mmHg (right arm) and 150/90 (left arm). Pulse rate was 80 beats/min.

A systolic murmur was heard with maximal loudness parasternally in the fourth intercostal space. No other murmurs were present. Arterial pulsations of the femoral artery and in the feet were weak but present. Blood pressure in the legs was so low that the resident in charge was unable to measure a reliable blood pressure value. Laboratory examination was unremarkable. Electrocardiography was normal without any signs of left ventricular hypertrophy. Echocardiography showed a bicuspid aortic valve.
Because of the bicuspid aortic and the very low leg blood pressure, an magnetic resonance imaging (MRI) angiography of the thoracic aorta was performed. This examination confirmed the presumed diagnosis of a coarctation of the aorta with extensive distended collateral blood vessels. The patient was scheduled for balloon angioplasty with placement of an intravascular expandable stent.

Case report 2

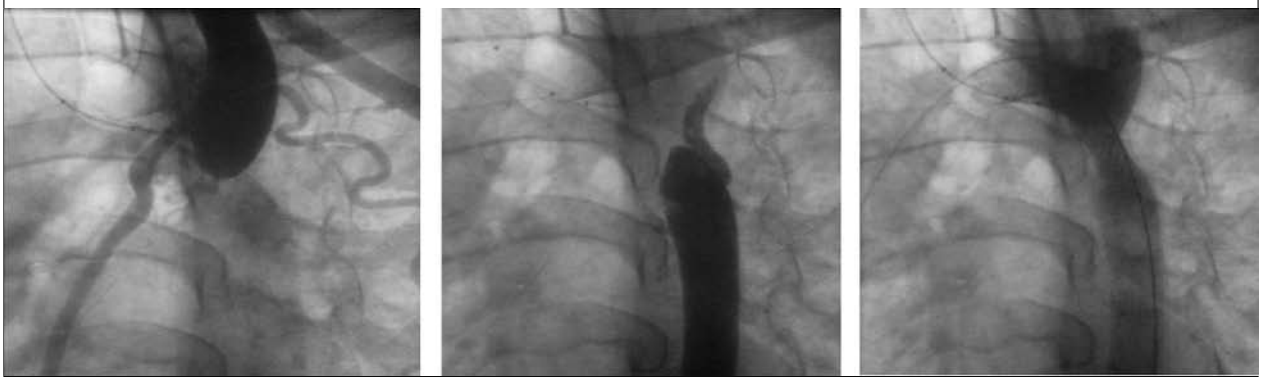
The second patient, a 31-year-old man with hypertension, was referred to our department by his family physician in 2003 because of therapy-resistant hypertension. In 1990 he was diagnosed with hypertension and in 1998 a diagnosis of primary hypertension was made by an internist in another hospital. The patient was subsequently treated with captopril and hydrochlorothiazide. Apart from an occasionally occurring pressing sensation in his head he reported no other symptoms. No other risk factors for cardiovascular disease were present. The family history was negative for renal disease, diabetes or cardiovascular disease except for his grandmother who had hypertension. His medical history only revealed a traumatic contusion of the left brachial plexus in 1988. On examination, blood pressure was 160/100 mmHg with a pulse rate of 70 beats/min. A systolic murmur was heard over all cardiac areas with maximal loudness at the second intercostal space on the left and in the neck. No murmurs were present over the abdominal and femoral arteries. The arterial pulsations in the feet were noted as normal but the presence of the femoral pulses was not described on the chart.

The results of the routine laboratory examinations were unremarkable. After stopping his antihypertensive drugs for two weeks, plasma aldosterone and renin concentrations were within normal limits. After administration of 50 mg captopril, plasma renin rose from 32 mE/l to 114 mE/l, which raised the suspicion of renal artery stenosis. An electrocardiogram showed a regular sinus rhythm with negative T waves in leads III and AVF and pathological Q waves in I and AVL. Echocardiography excluded left ventricular hypertrophy but disclosed a bicuspid aortic valve. At renal computed tomography (CT) angiography, the renal arteries were patent without any stenosis but extensive distended collateral blood vessels were observed in the musculus rectus abdominis and in the upper abdominal area. This finding raised the suspicion of a more proximal aortic flow obstruction such as an aortic coarctation. Re-examination of the patient showed that the femoral pulses were weak and that arm systolic blood pressure amounted to 154 mmHg while this was only 104 mmHg in the leg. Additionally, he reported that as a child, he had always had fitness problems with various sport activities such as jogging, soccer and field hockey. In contrast, he could perform in gymnastics very well. This disparity fits with the final diagnosis of coarctation of the aorta which was definitely established by CT angiography of the thoracic aorta. The patient was scheduled for balloon angioplasty with placement of an intravascular expandable stent (*figure 1*).

DISCUSSION

In the general population, only 5% of patients with hypertension have an underlying disorder causing the hypertension. The younger the patient, the higher the chance of secondary hypertension. Of all causes of secondary hypertension, the prevalence of coarctation of the aorta in adult patients in the primary care setting is probably less than 0.2%.[3]

Figure 1. *Antegrade (left panel) and retrograde (middle panel) angiography of the thoracic aorta was necessary due to the pinpoint stenosis of the severe aortic coarctation, right panel shows the aorta after expandable stent placement*



Although this might be higher in secondary or tertiary referral centres, it is still an extremely rare cause of hypertension. Yet, an early diagnosis is important because if left undiagnosed and untreated, premature cardiovascular accidents such as heart failure and rupture of the aorta may develop at a young age. Life expectancy is considerably reduced and 70 to 90% of the untreated patients die before the age of 50 years.[4,5]

The clinical manifestations of coarctation may vary between individuals and are highly dependent on the degree of the aortic obstruction and the presence of associated anomalies such as a bicuspid aortic valve.[6] Many adult patients may be asymptomatic except for hypertension and its related symptoms such as headache. The principal clinical signs leading to an early diagnosis are weak femoral pulses and a lower systolic blood pressure in a leg as compared with that in the arm (difference >20 mmHg). Since coarctation is frequently associated with extensive collateral circulation, cardiac murmurs originating at the upper sternum with bilateral radiation to the back are often heard. On a chest radiograph, notching of several posterior ribs can be seen, due to the increased collateral flow through the intercostal arteries (*figure 2*).

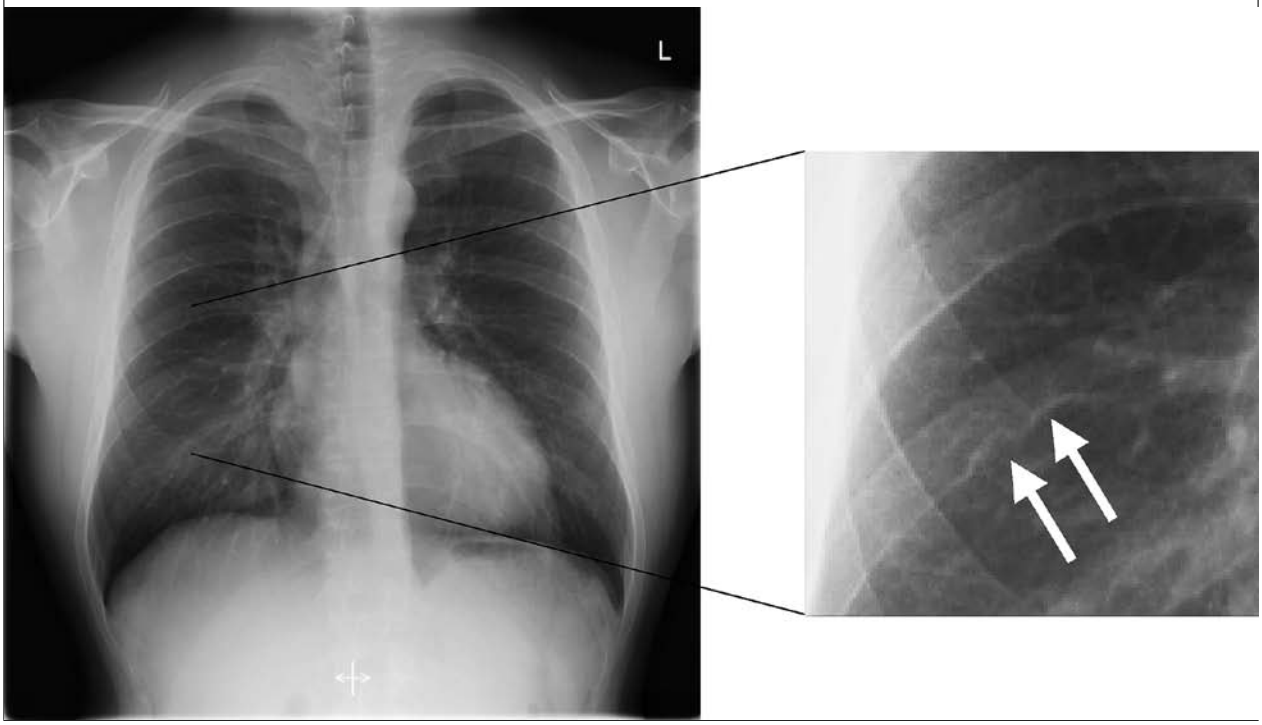
Echocardiography with colour Doppler flow mapping can be used to estimate the degree of stenosis and it facilitates screening for other cardiac anomalies such as a bicuspid aortic valve. To obtain precise anatomical information and to visualise the collateral vessels, CT angiography or magnetic resonance angiography can be used.[7]

Primary treatment of coarctation is repair by either surgery or balloon angioplasty alone or with placement of an expandable intravascular stent. Although surgery and angioplasty are both successful, a higher incidence of aneurysm formation has been reported with angioplasty.[8] A previous study by Zabal *et al.* suggested a better outcome and lower risk of aneurysm formation when a stent was used during angioplasty.[9] Carr *et al.* also found a higher incidence of recurrence and reintervention rates after endovascular therapy.[10] Additionally a recent study by Oliver did not find a significant difference in the prevalence of aortic complications with patients treated by surgery or patch graft aortoplasty.[11] However, large series of patients treated with angioplasty with or without stent placing are lacking. Therefore the role of primary balloon angioplasty with or without placement of a stent remains unsettled.

Recoarctation, paracoarctation aneurysm, and endocarditis are the major long-term complications of repair.[12] Although after successful repair blood pressure falls in the long term, the prevalence of hypertension remains high (33 to 42%) if surgery is performed after the age of 14 years.[13,14] Both our patients had a decrease in blood pressure after stent placement. Our first patient is still on 50 mg metoprolol and at his last visit his blood pressure was 140/80 mmHg. Our second patient is still normotensive and off drug treatment two years after stenting of the aorta.

Survival after repair is influenced by the age of the patient at the time of surgery and is independently related to the coexistence of a bicuspid aortic valve. Survival rate decreases

Figure 2. *Chest X-ray showing the rib notching on the right side (arrows)*



with older age at the time of repair but even in adult patients correction should be carried out as soon as possible.[15]

In our patients who presented with hypertension, the total delay until the definite diagnosis amounted to five and 13 years, respectively. More importantly, the essential signs of a coarctation were not disclosed because of repeatedly deficient physical examinations. Unfortunately, this is not at all unusual.[16] In the first case, the patient insisted on specialist referral whereas the family physician wanted to initiate medical treatment for hypertension. Measurement of blood pressure in a leg would have raised the suspicion of a coarctation as a cause of the high blood pressure. Also the presence of the cardiac murmur should have been a compelling reason for specialist referral. This could have prevented the five-year delay of the diagnosis and appropriate treatment. The combined finding of a cardiac murmur and the very low blood pressure in the legs resulted in a fast and correct diagnosis.

The second patient illustrates that even the finding of a cardiac murmur and a bicuspid aortic valve did not lead to the proper diagnostic direction in a third referral centre. Due to nonadherence to our own diagnostic protocol, measurement of leg blood pressure was omitted by the resident who saw the patient initially in our clinic, causing another delay of nine months. Leg blood pressure measurement would certainly have pointed to the correct diagnosis.

Measurement of both leg and brachial systolic blood pressure is a mandatory step in the initial evaluation of every young patient (<50 years) with unexplained hypertension especially when murmurs or weak femoral pulsations are present. Although aortic coarctation is a rare condition, the crucial physical diagnostic step leading to a diagnosis is not only easy and patient-friendly but also cheap. If leg blood pressure is less than 20 mmHg lower than arm blood pressure, a coarctation of the aorta is extremely unlikely. Conversely, if leg blood pressure is more than 20 mmHg lower than brachial blood pressure, a diagnosis of coarctation of the aorta should be considered immediately since early and appropriate treatment of this cause of hypertension does improve life expectancy by reducing premature cardiovascular complications. However, despite this improved therapy, life expectancy remains less than that of the general population.

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CASE REPORT

T-cell large granular lymphocytic leukaemia: successful response to 2-deoxycoformycin

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ABSTRACT

We report a 25-year-old woman with T-cell large granular lymphocytic leukaemia presenting with severe neutropenia, anaemia and recurrent infections with a chronic disease course. Immunophenotyping showed an expansion of $CD3^+$, $TCR\gamma\delta^+$, $CD4^-$, $CD5^+$, $CD7^+$, $CD8^+$, $CD57^+$ large granular lymphocytes. Clonality was demonstrated with T-gamma polymerase chain reaction analysis which revealed clonal rearrangement of the TCRγ chain gene. Cyclosporine, granulocyte colony-stimulating factor, methothrexate and a combination of cyclophosphamide, vincristine and prednisolone failed to correct the neutropenia and the anaemia. Finally, treatment with 2-deoxycoformycin resulted in both clinical and haemotological complete responses, despite molecular evidence of the persistence of the abnormal T-cell clone.

KEYWORDS

2-deoxycoformycin, anaemia, $CD8^+$, neutropenia, T-cell large granular lymphocyte

INTRODUCTION

T-cell large granular lymphocytic leukaemia (LGL) is an indolent leukaemia characterised by the clonal proliferation of morphologically distinct lymphocytes named for their typical large azurophilic cytoplasmic granules.[1] The majority of cases are of T-cell origin, mainly with a $CD3^+$, $TCR\alpha\beta^+$, $CD8^+$ immunophenotype, and a minority derived from $CD3^-$ NK cells. Leukaemic LGL may also be $CD3^+$, $TCR\gamma\delta^+$, being $CD4^-$, $CD8^+$ or $CD4^-$, $CD8^-$.[2] Clinically, T-LGL leukaemia is characterised by chronic neutropenia or other manifestations including rheumatoid arthritis and anaemia. Splenomegaly and lymphadenopathy is extremely rare. Although the natural history of T-LGL is relatively benign, its clinical course may be complicated by recurrent neutropenic infections and severe anaemia.[2-4] Unlike B-cell malignancies, there is no standard treatment for patients with T-LGL leukaemia. Treatment approaches have included growth factor, splenectomy, cytotoxic therapy (alkylating agents, purine analogues) immunosuppressive drugs (cyclosporin A (CSA), methotrexate (MTX) and monoclonal antibodies (alemtuzumab).[2-13]

Here we describe a patient with T-LGL leukaemia who remained refractory to various treatments with CSA, granulocyte colony-stimulating factor (G-CSF), MTX and a combination of cyclophosphamide, vincristine and prednisolone, respectively. Finally, a trial with 2-deoxycoformycin (2-DCF) resulted in both clinical and haematological complete responses, despite the molecular evidence for the persistence of the abnormal T-cell clone.

CASE REPORT

A 25-year-old woman was referred to the Department of Haematology in May 2000 for the evaluation of neutropenia and anaemia. She had a previous one-year history of fatigue and arthralgias. Physical examination showed splenomegaly 2 cm below the costal margin. CT scans of the chest, abdomen and pelvis showed only splenomegaly, but no evidence of hepatomegaly or lymphadenopathy. Peripheral blood counts at diagnosis were: white blood cells (WBC) 2 x 10^9/l, neutrophils 0.4 x 10^9/l, lymphocytes 1.6 x 10^9/l, platelets 221 x 10^9/l, haemoglobin (Hb) 9.2g/dl, and haematocrit (Hct) 29%. Seventy percent of lymphocytes exhibited LGL morphology. Immunophenotyping of the peripheral blood lymphocytes by flow cytometry demonstrated $CD3^+$ (89%), $CD4^-$ (11%), $CD5^+$ (85%), $CD7^+$ (89%), $CD8^+$ (79%),$CD11c^-$ (3.2%), $CD19^-$

(2.6%), CD79a$^-$ (0.3%), TCR$\gamma\delta^+$ (59%), TCR$\alpha\beta^-$ (7.9%). Monoclonal rearrangement of T-cell receptor γ gene was detected on both the peripheral blood and bone marrow mononuclear cells, using polymerase chain reaction and heteroduplex temperature gradient gel electrophoresis.

The bone marrow aspirate showed an infiltration (56%) by LGL, and a bone marrow trephine biopsy revealed a slightly hypocellular marrow with normal megakaryocytes, an interstitial and micronodular lymphocytic infiltration, but rare granulocytic precursors. Serum immunoglobulin levels were normal. Antinuclear antibodies and antineutrophil antibodies were negative. Rheumatoid factor level was elevated (13,000 IU/ml; normal 35 IU/ml) but the radiographic examination of the joints did not show any soft tissue swelling, joint effusion and/or any bony erosion. Cytogenetics on bone marrow metaphases was normal. Based on these findings, the diagnosis of T-LGL leukaemia was made in our patient.

Although the clinical course was satisfactory for six years, sudden drops in her already decreased neutrophils caused concomitant recurrent bacterial infections such as cellulitis, pharyngitis, sinusitis, respiratory tract infections and perirectal abscesses.

She had no compatible sibling donor for bone marrow transplantation; in view of her young age, she was given the following treatment schedule from May 2000 to April 2006: CSA 5 mg/kg/day for six months which increased the WBC count to 3 x 10^9/l, neutrophils to 1.5 x 10^9/l, Hb to 10.9 g/dl and Hct to 33%. Six months later, CSA was withdrawn because of significant renal function impairment. Readministration of CSA at a dose of 3 mg/kg/day was without effect. She was also unresponsive to G-CSF 5 µg/kg/day for nine months and to MTX 10 mg/m^2/week orally for six months respectively. She therefore received six cycles of a combination of cyclophosphamide (750 mg/m^2 iv day 1), vincristine (1.4 mg/m^2 iv day 1), and prednisolone (100 mg/day x 5 orally). Cycles were repeated every 28 days. The patient had only minor and transient benefit from this treatment. In March 2006, she was scheduled to receive six cycles of 2-DCF (6 mg/m^2 iv every two weeks, six doses). Before the initiation of the treatment the patient's peripheral blood values were as follows: WBC 1.4 x 10^9/l, neutrophils 0.3 x 10^9/l, lymphocytes 1.1 x 10^9/l, platelets 312 x 10^9/l, Hb 8.2 g/dl, and Hct 25%. Bone marrow trephine biopsy showed interstitial and micronodular lymphocytic infiltration with LGL. After the start of the treatment a slight increase in the neutrophil count was observed, and after the completion of the third cycle of DCF, the patient had a normal absolute neutrophil count (2.3 x 10^9/l), and a physical examination was normal with no splenomegaly. On the last follow-up on April 2007, the patient was very well. A complete blood count showed: WBC 4.7 x 10^9/l, neutrophils 3.3 x 10^9/l, lymphocytes 1.4 x 10^9/l, Hb 14.1 g/dl, Hct 41.5% and platelets 330 x 10^9/l. Rheumatoid factor level was within normal limits (20 IU/ml). After this treatment T-LGL clonality was still persisting.

DISCUSSION

We describe a case of T-LGL leukaemia (CD3$^+$, TCR$\gamma\delta^+$, CD4$^-$, CD5$^+$, CD7$^+$, CD8$^+$, CD57$^+$ phenotype) associated with neutropenia, anaemia, and recurrent infections during the course of the disease. Most patients with T-LGL leukaemia have CD3$^+$, TCR$\alpha\beta^+$, CD4$^-$, CD8$^+$ phenotype. Very rarely leukaemic LGL may also have CD3$^+$, TCR$\gamma\delta^+$, CD4$^-$, or CD8$^+$. These TCR$\gamma\delta^+$ cases seem to have similar clinical presentations to TCR$\alpha\beta^+$ cases, including neutropenia and arthritis.[14-18]

Immunomodulation is the mainstay of T-LGL leukaemia treatment with recurrent infections and symptomatic anaemia as the most common indication for therapy. But symptomatic thrombocytopenia, progressive lymphocytosis and splenomegaly are also indications for treatment. An optimal therapy for T-LGL leukaemia patients has not yet been defined. Because of the rarity of T-LGL leukaemia, no prospective clinical trials have been reported and current treatment strategies are based on anecdotal case reports and small retrospective studies.[4-13]

Agents such as CSA, MTX, and prednisolone have been used with varying success rates.[4,7,9,10] First-line, single agent therapy with CSA is effective for correcting cytopenia in some patients, but its nephrotoxicity remains a problem for long-term treatment. Furthermore, CSA does not affect the abnormal LGL even in responding patients.[7,9] Our patient initially responded favourably to CSA treatment, but renal toxicity led to its withdrawal. Reinstitution of CSA at a lower dose was ineffective. The benefit of haematopoietic growth factor such as G-CSF, granulocyte-macrophage colony-stimulating factor (GM-CSF) or erythropoietin is controversial.[5-7] In our patient G-CSF administration was ineffective. More encouraging results in the treatment of patients with T-LGL leukaemia have been reported with the use of low-dose MTX with or without prednisolone. The majority of patients treated with this immunosuppressive drug entered complete clinical remission.[4,8,10] Unfortunately, our patient failed to respond to MTX.

Low-dose oral cyclophosphamide and/or prednisolone therapy is an effective treatment for some patients with T-LGL leukaemia. In our case, combined cyclophosphamide, vincristine and prednisolone resulted in minimal and transient responses in anaemia, neutropenia and splenomegaly.

Some studies continue to support the utility of purine analogues.[4,7,11-13] There have been a few cases of T-LGL leukaemia achieving a long-term clinical and haematological remission with DCF, despite molecular evidence of the persistence of the abnormal T-cell clone.[11-13] Our patient responded both clinically and haematologically to DCF treatment, with the persistence of the abnormal T-cell clone.

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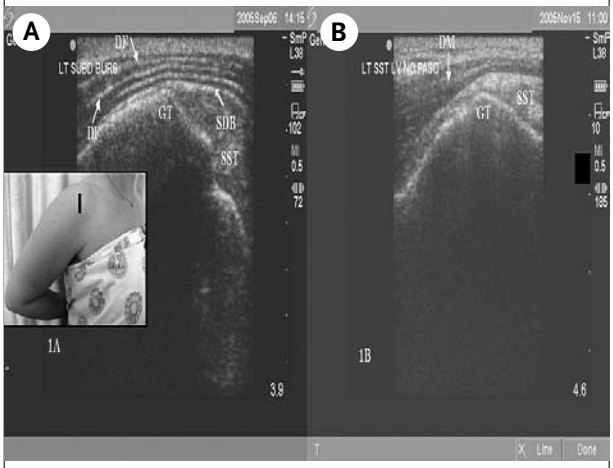
LETTER TO THE EDITOR

US imaging of shoulder fasciitis due to polymyalgia rheumatica

Fascia and soft tissues, which are rich in collagen, receptors of pain and capable of significant distention, may be targets of autoimmune inflammatory diseases, causing morning stiffness, swelling, severe pain and limitation in movement. Ultrasound (US) is a very effective method for imaging soft tissues. The most frequent US soft tissue alterations in patients with polymyalgia rheumatica (PMR) are subdeltoid bursitis, tenosynovitis of the biceps tendon, and glenohumeral synovitis.[1] US imaging of another soft tissue disease, eosinophilic fasciitis, has also been described recently, but without a healthy control group.[2] We observed a thickened deltoid fascia (DF) by US study in patients with active PMR, which has not been reported previously. The aim of the study was to describe sonographic data of fasciitis due to PMR. Portable sonography (Sonosite-Titan, 5-10 mHz, L38) was performed on 14 patients with PMR (Chuang-Healey criteria, normal creatine kinase, differentiating PMR from macrophagic myofasciitis[3]) (aged 65.4 ± 6.5 years, BMI 25.4 ± 1.6 kg/m^2). Thickness of DF (coronal view) was measured and compared with ten healthy controls (7 women, 3 men, aged 61.5 ± 11.8 years, BMI 27.7 ± 5.1 kg/m^2). Coronal view of patients with PMR showed a 'two tram tracks' appearance (*figure 1A*): two thickened DF and two leaflets of subdeltoid bursitis separated by a hypoechoic layer. The shoulder position in internal rotation, extension and adduction for investigation was chosen for better visualisation of the subdeltoid bursa (*figure 1A-B*). Thickness of DF for active PMR was 1.68 ± 1.37 mm compared with controls (0.83 ± 0.25 mm; p=0.047). We observed other US characteristics of the fasciitis: fascial cleavage, easy detection of the thickened fascia, increased echogenicity, perifascial hypoechoic layers, and multiple hyperechoic lines of thickened perimysial tissue inside the deltoid muscle. After two months of CS therapy, the DF became undistinguished from controls (0.91 ± 0.28; p=0.1) (*figure 1B*). BMI of patients with PMR and controls did not differ (p=0.19). US imaging is an effective method to visualise, confirm and follow the course and therapy of fasciitis in patients with PMR.

Figure 1. *Prominent thickening of deltoid fascia (deltoid fasciitis) and subdeltoid bursitis with 'tram track' appearance are seen (A), which disappeared after two months of corticosteroid therapy (B) (Coronal view, shoulder in internal rotation, extension and adduction)*



DF = deltoid fascitis; SDB = subdeltoid bursitis; GT = great tuberositas; SST = supraspinatus tendon.

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PHOTO QUIZ

A patient with subdiaphragmatic air

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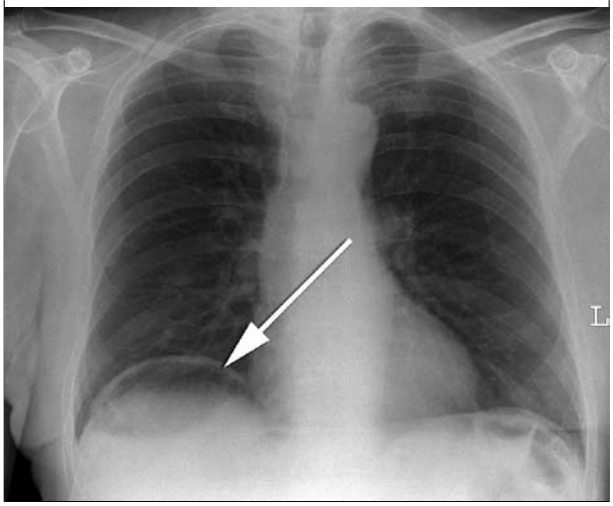
CASE REPORT

A 66-year old man presented to the Emergency Department with fever of three days' duration and nausea. He was being treated with combined radiotherapy and chemotherapy for a recently diagnosed locally advanced hypopharyngeal carcinoma. Two weeks before admission, a percutaneous endoscopic gastrotomy (PEG) tube was inserted as a routine procedure to ensure adequate nutrition during chemoradiation. The procedure was uncomplicated, but a 2-cm large gastric ulcer was diagnosed. Proton pump inhibiting drugs were prescribed and an appropriate feeding regimen was started.

On presentation, careful history taking did not provide clues to the focus of his fever. Examination of the abdomen was unremarkable. A review of the operation site demonstrated that the tube was firmly anchored in position with no evidence of leakage. Blood chemistry revealed a neutrophil count of 9.9 x 10^9/l two weeks after the first dose of cisplatinum chemotherapy (100 mg/m^2). C-reactive protein was 311 mg/l. A posterior-anterior chest radiograph was suggestive of free intraperitoneal air under the right hemidiaphragm (*figure 1*).

Figure 1. *Posterior-anterior chest radiograph, suggestive of free intraperitoneal air under the right hemidiaphragm*



WHAT IS YOUR DIFFERENTIAL DIAGNOSIS?

See page 90 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (ON PAGE 89)

A PATIENT WITH SUBDIAPHRAGMATIC AIR

DIAGNOSIS

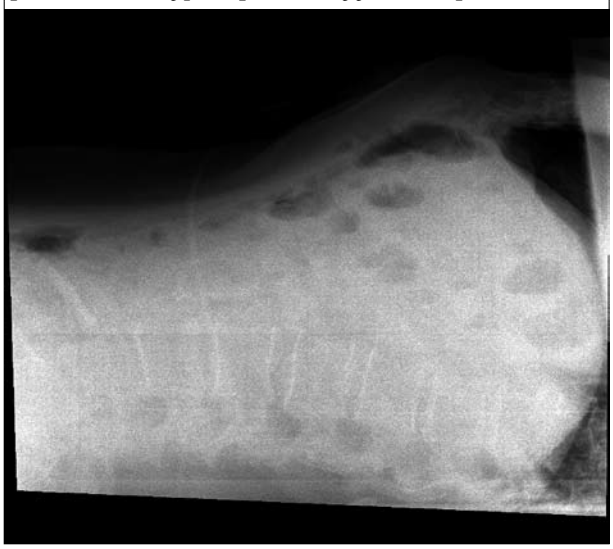
Air observed under the diaphragm on standard chest radiograph can have many aetiologies, some of which require urgent surgical intervention. In our patient, the combination of fever, nausea, leucocytosis, and elevated C-reactive protein made us consider the possibility of perforation of his previously diagnosed gastric ulcer. In the absence of specific abdominal symptoms consistent with peritonitis, however, other causes were explored.

Pneumoperitoneum is a recognised early complication of PEG tube insertion and was included in our differential diagnosis. This complication is seldom diagnosed, although its prevalence is reported at up to 25% if specifically looked for.[1] Free air usually resolves spontaneously in one or two days and surgical intervention is rarely required. A single case report, however, has described pneumoperitoneum developing more than six weeks after PEG tube insertion, with vomiting as initial presenting symptom.[2]

Demetrius Chilaiditi first described interposition of the transverse colon between the liver and the diaphragm.[3] This finding could be mistaken for pneumoperitoneum resulting in unnecessary exploratory laparotomy. Distinction between free air and air in a loop of bowel can be made based on visible haustra or plicae circulares.[4] Also, changing the position of a patient with Chilaiditi's sign will not change the position of the abdominal air. Abdominal radiographs in lateral position or abdominal computed tomography can thus be used to distinguish both entities. To verify the presence of free intraperitoneal air in our patient, an abdominal radiograph in left lateral position was taken (*figure 2*). This examination did not show any evidence of free air. Thus, the diagnosis of Chilaiditi's sign was made. In addition, our patient showed evidence of concomitant urinary tract infection which was treated with antibiotics.

Chilaiditi's sign may coincide with symptoms such as nausea, vomiting, distension, abdominal pain, and constipation, but is often asymptomatic. Treatment, if required, consists of bowel decompression. Thus, pneumoperitoneum on chest radiograph can be an indication for immediate surgical exploration, but it is important to realise that air observed under the diaphragm on chest radiograph may have other aetiologies that do not mandate urgent intervention. Chilaiditi's sign must be included in the differential diagnosis in these patients, especially in the absence of specific abdominal symptoms consistent with peritonitis.

Figure 2. *Abdominal radiograph in left lateral position, to verify the presence of free intraperitoneal air*



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Netherlands
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PHOTO QUIZ

Severe arch vessel disease

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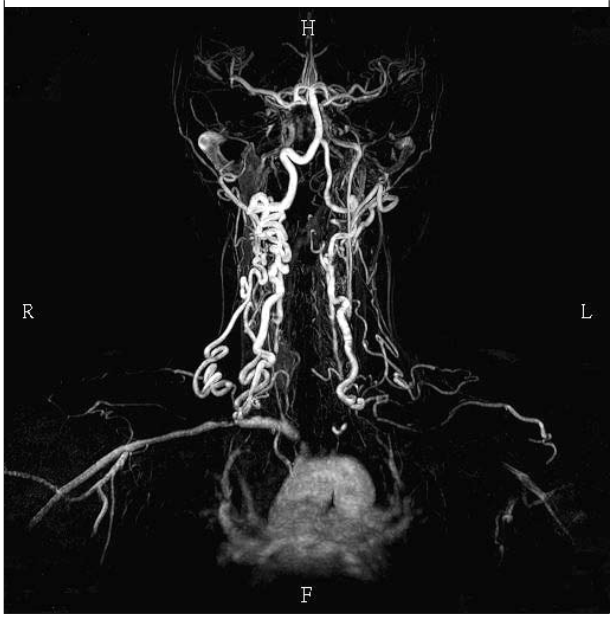
CASE REPORT

A 41-year-old woman was hospitalised due to sudden onset of blindness of the right eye for three hours. She had been fit before, except for suffering from episodes of transient visual defect lasting a few seconds. She was alert but looked ill. Physical examination revealed a blood pressure of 70/50 mmHg in the upper limbs and 110/70 mmHg in the lower ones. Neither of the carotid pulses were palpable. Heart, lungs, and abdominal examinations were unremarkable. She was anaemic with a haemoglobin of 5.3 mmol/l. Chest radiographs revealed normal cardiac size with tortuosity of the aorta. Magnetic resonance angiography of the aortic arch vessels was carried out (*figure 1*).

Figure 1. *Magnetic resonance angiography of the aortic arch vessels*



WHAT IS YOUR DIAGNOSIS?

See page 92 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (ON PAGE 91)

SEVERE ARCH VESSEL DISEASE

DIAGNOSIS AND TREATMENT

The magnetic resonance angiography showed total occlusion of the bilateral common carotid and left subclavian arteries. The remaining critically stenotic brachiocephalic artery supplied the entire circulation of brain via complex collaterals. The clinical features and vascular imaging were consistent with Takayasu arteritis (TA). Because of the high risk of hypoxic cerebral injury associated with the surgical techniques used in revascularisation based on the anatomic findings, we decided to use percutaneous transluminal angioplasty (PTA) for the treatment of the critical stenosis of the brachiocephalic artery (*figure 2A*). The lesion was first dilated with a 4.0 x 20 mm balloon. An 8.0 x 17 mm Express LD stent (Boston Scientific, Natick, MA, USA) was then successfully deployed at the stenotic lesion (*figure 2B*). The patient did not develop complications during the procedure. She was discharged after a hospitalisation of one week. There was no neurological dysfunction noted during one-year clinical follow-up.

REMARKS

Cardiac, renal and central nervous system vascular diseases are the principal causes of morbidity and mortality in TA and the mortality rate may be as high as 35% during five-year follow-up.[1] Currently PTA is regarded as a safe and effective modality of treatment in Takayasu's disease. Most of the vascular lesions in TA are short, with relatively large vessel diameter, which are the ideal target lesions for PTA. However, the rate of vascular restenosis in Takayasu's disease treated by balloon angioplasty is much higher than that observed in atherosclerotic lesions.[2] Bali *et al.* followed six patients with Takayasu's arteritis treated with aortic stenting for six months. No significant instent restenosis was noted among them.[3] Sharma and his colleagues showed that the instent restenosis rate was about 13.3% (2/15) in patients with Takayasu's disease.[4] This result is similar to that observed in atherosclerotic lesions. However, large-scale and long-term prospective studies are needed in order to clarify this point.

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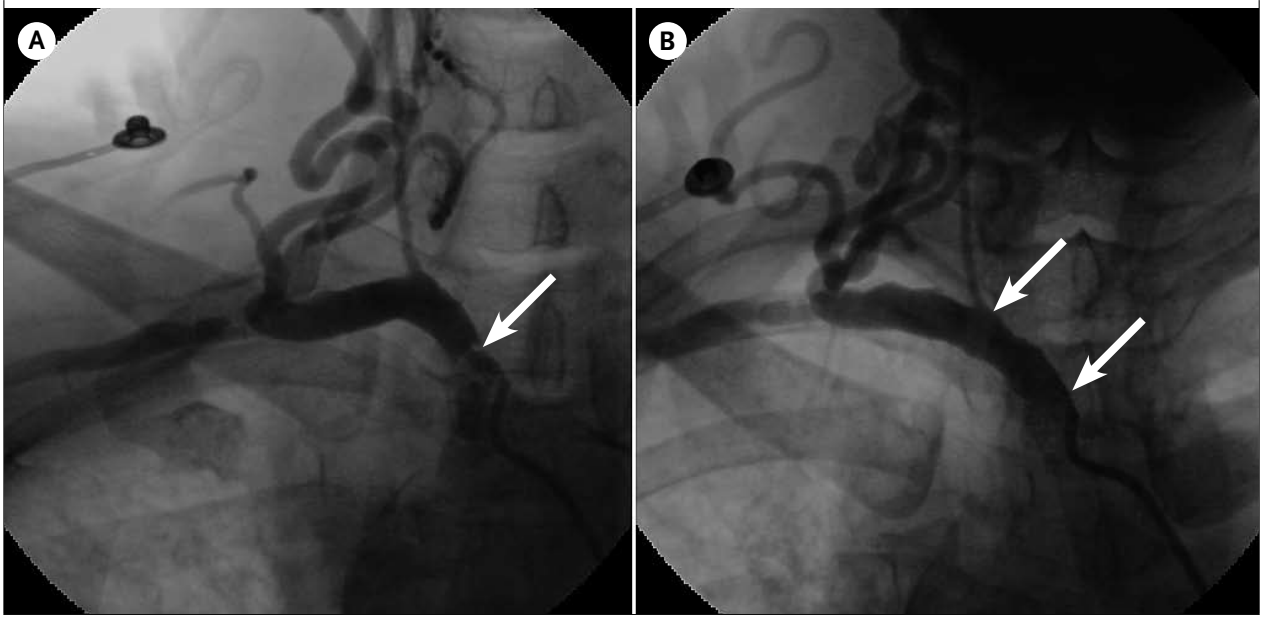
Figure 2. *(A) Angiography showed a critical stenosis (arrow) over brachiocephalic artery and absence of right common carotid artery, (B) an 8.0 x 17 mm stent (arrows) was deployed to the critical lesion with excellent angiographic results*



MONTHLY NJM ONLINE HITLIST

The table lists online hits for all articles published in the November issue of the *Netherlands Journal of Medicine* 2007 (available online on Pubmed since 19 November 2007).

Article	Hits
EDITORIALS	
Ageing and polymorbidity: is there a mismatch between the training of internists and the need?	136
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Total	**1984**

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Journal abbreviations should conform to the style used in the Cumulated Index Medicus. Examples:

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2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

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