TABU

3 | 2007

Lääketietoa Lääkelaitokselta

Läkemedelsinformation från Läkemedelsverket, Finland

Drug information from the National Agency for Medicines, Finland

På svenska | Översättning Mats Försskåhl

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Editorial

Pharmaceutical policy not yet incorporated into the government programme

The aims of the Second Government Programme[1] of Prime Minister Matti Vanhanen do not include an integral part known as the Pharmaceutical Policy. Medicines, and not merely their costs, are nevertheless mentioned. The Government Agenda may also be read and interpreted with respect to the issues omitted.

For the last couple of decades government programmes have only superficially touched upon the subjects of medicines and pharmacotherapy[2]. If pharmaceutical issues have been included at all in the programmes, the aims have been set from the standpoint of cutting the cost of medicines. This is understandable. According to the number of prescriptions, the increase in Finland in 1993–2006 reached 45%, and measured by DDD consumption the increase was 52%. At the same time the value of pharmaceutical sales increased by 171% and the total costs of refunds by 193 %.

The section discussing the welfare policies of the present government also focuses when dealing with pharmaceutical issues on the cost-cutting exercises. It is suggested that this should be done by reforming the drug reimbursement system. Special emphasis is laid on the reimbursement of the cost of new drugs, which ought to be based on their cost-effectiveness in health care. The challenge is increased by the ageing of the population, especially as the aim is to safeguard the right of the elderly population to good care and to create a fairer payment ceiling system to improve the situation of the big consumers of services and medicines.

Reformed policies in the government programme include the promoting of safe pharmacotherapies and the safeguarding of wide-ranging pharmaceutical services. Firstly, a novelty in these political aims is that the objective is pursued by drawing up a clear content of issues, albeit at a rather general level. Secondly, the fact that the use of money and costs are not tied up to the same context also presents a novel approach. Even though the concrete content of aims of a more general nature does not often emerge until the government period progresses, it is presumed that, at least, the government will not embark on measures, which would jeopardise these general aims as included in the government programme. Safe pharmaceutical care and wide-ranging pharmaceutical services make up good corner stone material for any programme.

About which issues does the government programme fall silent? Government programmes appear to be made up of issues in need of necessary reform at the time, about which the political parties can then come to an agreement. No programme can incorporate all the issues, and, to be fair, novel issues are constantly emerging. During this government period we are also likely to see several pharmaceutical issues debated in public and on the desks of the decision-makers. These may include, for example, a two-channel financing of drugs, guidelines for rational prescribing of drugs, pharmacy fee and pharmacy licensing systems, sales of OTC drugs and need for the fine tuning of the pharmaceutical administration.

The most frequently used words in the government programme describe aims that start off with an innovation. Immediately at the beginning of its term the government will prepare a national innovation strategy. In this context it would also be right to evaluate the promotion of drug innovations on national premises. Utilisation of the Finnish resources of scientific know-how should be improved in order to create innovative industrial and commercial success stories. This would also support the EU pharmaceutical sector innovation policies.

The consumption of drugs and the importance of pharmaceutical issues in health care will increase in the years to come. The present government programme refers to at least 20 different sectors of its policies. Pharmaceutical services as a whole contains several positive opportunities. The pharmaceutical policy will one day have to figure in the headlines and the programmes.

[1] http://www.vn.fi/hallitus/hallitusohjelma/fi.jsp
[2] Helmiö T. et al.: Medicines in focus of the health policies. TABU 5.2005, 58.

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Problems of pain assessment and management in dementia patients

Pain management in patients with dementia often raises three problem issues: identification of pain, choice of the most appropriate form of treatment and evaluation of response. A certain degree of sensitivity is required for a prescriber to suspect pain in a dementia patient as being the causative factor of behavioural changes, and new alternative methods of treatment may actually emerge as a result.

Pain in dementia patients is under-treated

Several studies have proven in unison that elderly dementia patients receive less treatment for their pain compared with other elderly patients suffering from diseases afflicting them with similar pain (1–8). The differences are seen, for example, in cancer (3), hip fracture (1, 4) and nursing home patients (2, 6). The difference has also been documented in a Finnish survey which states that, in comparison with other patients, pain in nursing home patients suffering from dementia is detected and treated to a lesser extent (7). The prevalence of pain in residents in longterm care settings also appears to decrease as the severity of the dementia increases (5). Indications of Alzheimer patients receiving less treatment than patients with, for example, dementia of vascular origin (8) have provided new incentives and prospects for studying the connections between cognition and pain.

Does the sensation of pain change in dementia?

Changes in the sensation of pain when ageing have been the subject of many studies and a general picture of a sort has eme-rged despite isolated contradictory research results (9–11). The peripheral pain threshold appears to rise slightly as the patients are growing older. In practice the change is minor and it is a result of impaired function of the A-delta fibres in the nervous system. The elderly also have a reduced tolerance of severe pain, even though mild irritation is not always perceived as pain as easily by them as it is by younger patients. Impairment of pain-modulating systems is thought to be the cause. Reduced perception of visceral pain is clinically widely proven. Impairment of the autonomic nervous system function is presumed to be the cause here, and may be the result of a number of diseases. It has proven difficult to ascertain the extent and manner in which pain sensations and reactions to pain change during cognitive impairment (12). According to studies by Benedett et al., the thresholds of sensory sensations of pain appear to be well retained in Alzheimer's disease, but the autonomic and affective responses (medial pain pathways) triggered by pain are reduced (12). In this situation even minor indications of pain-induced behaviour may be a sign of significant pain in patients with Alzheimer's disease. The changes may be even less distinct in other dementia-inducing brain diseases.

Pain assessment in dementia patients

Even patients with fairly severe dementia are usually able to express verbally the pain they suffer and to understand the questions posed in relation to their pain (13). In the case of very advanced dementia, observational methods and the interpretation of behavioural changes may have to be resorted to. The widely used *Resident Assessment Instrument* (RAI) system, with comparable tools developed for example for the needs of long-term institutional care and acute treatment (14, 15), also contains an assessment of the pain the patient is experiencing. The RAI system assesses the intensity and density of pain based on the patient's own report (and also on the assessor's report when difficulties with comprehension or communication are present).

Several different, but so far inadequately standardised, assessment tools have been developed for assessing the pain of patients with dementia and lack of communicative ability (16–18). The Pain Assessment in Advanced Dementia Scale (PAINAD) is one of these tools, based on the structural observation of behavioural changes caused by pain (19). The pain assessment tool PAINAD consists of five observation categories: breathing, vocalisation, facial expressions, body language and consolability. Each category contains a scale of three points (0–2) for the behavioural changes caused by the pain (Table 1).

Table 1. *Pain Assessment in Advanced Dementia Scale (PAINAD-scale).*

	0	1	2
Breathing	Normal and unnoticeable.	Breathing occasionally troblesome. Short periods of hypervetilation.	Breathing loud and troublesome. Long periods hyperventilation. Cheyne-Stokes-type of breathing.
Uttering	No uttering of sounds. Content uttering of sounds.	Occasional wailing or moaning. Moaning or complaining, quiet talk.	restless shouting. Loud wailing or moaning. Crying.
Expressions	Smiling or expressionless.	Sad. Frightened. Severe.	Grimacing.
Body language	Restful.	Tense. Anxious walking. Restless movements.	Rigid. Hands in a fist. Knee up. Pulling or pushing. Jerking.
Consolability	No need to be consoled.	A sound or a touch districts the attention elsewhere or calms down.	Consolation, distraction of attention or calming do not have an effect.

Pain assessment is carried out during observation periods lasting for about 5 minutes. The pain is assessed by scoring total points in between 0 and 10, where 0 indicates a pain-free state and 10 the most severe pain. The level of pain is assessed before and during the administration of treatment.

We carried out a survey recently into the prevalence of pain in elderly hospital patients with dementia in both outpatient hospital clinics and long-term care settings in Helsinki (20). In emergency hospital settings (n=95), according to the RAI-AC scale, 51% of the patients had suffered from pain during last 24 hours (Table 2). Using the PAINAD scale, however, indications of pain were observed in 47% of patients at rest and 77% of patients during administration of treatment. The two scales conformed with one another at the state of rest in only a little over half of the patients. Almost every alternate person among those judged as pain-free by the RAI-AC scale were found to experience pain when measured against the PAINAD scale. During the administration of treatment, as many as more than two thirds of those patients judged as pain-free by the RAI-AC scale were apparently suffering from pain when assessed against the PAINAD scale. The patients' cognitive level was not specified in the survey, but in emergency hospital settings the patients were, as a rule, able to answer questions about pain in the RAI system by themselves.

Patients in long-term care settings (n=202) were, as a rule, totally unable to answer questions about pain on the RAI-LTC scale, and the results were based on the joint assessment made by the patients' nurses. Measured by the PAINAD scale pain at rest occurred in 43% and pain during administration of treatment in 75% of the patients. As for the daily pain, the scales agreed in only about a third of the patients, and the agreement between the scales otherwise was over 50% as it was with acute geriatrics ward patients. The proportion of patients suffering from pain when measured by the PAINAD scale during rest was about 40% and during the administration of treatment was about 70% of those judged as pain-free by the RAI-LTC scale. A majority of those judged as pain-free at rest by the PAINAD scale appeared to suffer from pain during the administration of treatment. In a small proportion of these patients the pain during the administration of treatment was in fact very

Table 2. *Recording of pain with the PAINAD scale at rest, during treatment measures, and in the RAI system (%).*

	PAINAD at rest		PAINAD during treatment		Total pain in RAI
	Pain	No pain	Pain	No pain	
Pain in acute geriatry in-patients during the previous 24 hours (n = 95)					
Pain in RAI	25,3	25,3	43,2	7,4	51
No pain in RAI	22,1	27,4	33,7	15,8	49
Total pain in PAINAD	47	53	77	23	100
Pain in long-term hospital patients less often than daily (n = 202)					
Pain in RAI	23,8	21,8	39,1	6,4	46
No pain in RAI	19,3	35,1	35,6	18,8	54
Total pain in PAINAD	43	57	75	25	100
Pain in long-term hospital patients daily during the previous week (n = 202)					
Pain in RAI	7,9	5,9	12,4	1,5	14
No pain in RAI	35,1	51	62,4	23,8	86
Total pain in PAINAD	43	57	75	25	100

severe. Nearly 95% of the patients assessed as pain-free during the administration of treatment were also classed as pain-free at rest.

The pain assessments by the RAI system and the PAINAD scale therefore differed significantly from one another in elderly patients with mild in acute care or severe dementia in long term care. A survey of the results of the pain measurement scales separately shows that they both reported nearly every alternate subject in our material as suffering from pain at least weekly, but there was mutual agreement between the RAI system and PAINAD scale about classifying only about one in every four patients as suffering from pain. The PAINAD scale also found indications of pain during the administration of treatment in almost three out of four patients who had been judged as pain-free by the RAI system.

Interpretation of the results is also made difficult by the absence of an objective standard, called the golden standard, for the assessment of pain in patients with severe dementia. In these patients, however, the worldwide proof of the reliability and validity of the PAINAD scale is already encouraging (16–18). The introduction of the PAINAD scale and the carrying out of assessments during the administration of treatment, however, appears to increase the reporting of pain, which has resulted for example in the increased use of analgesics (21). In addition, the patient's own report has been considered inappropriate as a pain assessment method in patients with moderate or severe dementia, as the patients' own reports have been found to deviate distinctly from both the assessments made by the care personnel and the results obtained by the PAINAD scale (22). In the same way, the RAI system has been found to underrate the pain experienced by residents with cognitive impairment in long-term care settings (23). The survey shows that the pain-free state detected by the PAINAD scale especially during the administration of treatment would appear to give a fairly strong indication of the patient's true pain-free state. Nevertheless, further studies are required before the PAINAD scale can be widely recommended as the only pain assessment method in elderly patients with dementia.

The pain in dementia patients, too, is always a subjective experience; and all pain assessment methods are inadequate, especially in patients with an inability to communicate. Instead of pain, or together with it, the patient's behavioural changes may also have other underlying factors, such as thirst, need to go to the toilet, purposeless level of alertness, depression, psychosis or uncomfortable clothing. Behavioural changes in dementia patients may also vary considerably. It is recommended that while observational behavioural methods of pain assessment are being developed and evaluated in future, emphasis should be placed in several different observational sections on the scales by which behavioural changes are observed. Even though pain scales which structurally observe the behavioural changes can easily be considered to interpret the dementia patient's general discomfort as pain, the scales do nevertheless allow another opportunity to stop and look at the patient and to make a better assessment of the cause of the variation shown by the pain scale.

Should pain treatment be improved?

There are ethical reasons as such for making an effort also to alleviate pain in the case of dementia patients if a pain-free status cannot be guaranteed. However, very few controlled clinical trials have been carried out to test the effects of analgesic therapies on the pain behaviour of demented patients or on their other consequences. Two retrospective reviews have indicated an increase in analgetics use to be associated with a decrease in the use of antipsychotics (24, 25). The changed degree of agitation (*Cohen-Mansfield Agitation Inventory*) has been assessed in 25 dementia patients, judged as pain-free, who were given a placebo over a period of four weeks, followed by a small dose of morphine with a long-term effect for the subsequent four weeks (oxicodone 10 mg 1 x 2). Some of the agitation was presumed to be due to unidentified pain and the symptoms possibly to be alleviated by analgetic therapy. This did not happen, however, even though an observation fitting in with the hypothesis was, in fact, identified in a subgroup of the over 85-year-olds. It was speculated that only the oldest age group had received a dose of morphine which was adequately high. A corresponding. test was carried out with paracetamol, which was administered (at 3 x 1,000 mg) intermittently with a placebo, both of them in blind trials for a period of four weeks (27). During the course of analgetics the patients were moving about more and they were socially more active. Unpredictably, the symptoms of agitation were not decreased and the mental wellbeing was not improved. Neither was the use of antipsychotics diminished. On examining 39 dementia patients (MMSE 4.3 ± 5) with degenerative arthritis, there was no difference found in the treatment of pain between regular and as-required paracetamol medication (28). The daily dose of 2,600 mg used was nevertheless inadequate for reducing discomfort when compared with the placebo group. As with other issues, new, more extensive studies are urgently needed to review this one.

Literature: See page 7.

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Statin-induced myopathy: truly common or rare adverse reaction?

Large-scale clinical trials have shown that statins are effective and safe cholesterol lowering compounds (1-3). More recent data suggest that aggressive lipid lowering results in even greater reductions of atherosclerotic complications. Thus, more patients are titrated to higher doses of statins to reach the new aggressive goals of LDL-cholesterol reduction. However, aggressive treatment with high dosages has argued to increase the risk of statin-induced myopathy, therefore, identification of patients likely not to tolerate the treatment is of great clinical interest. Recently, several key papers have been published addressing statin-induced myopathy. One of the messages seems to be that the muscle effects are more frequent in clinical practise than estimated based on clinical trial reports. In a systematic review of randomised clinical trials Kashani et al. concluded that statin therapy is associated with a small excess risk of transaminase elevations, but not of myalgias, rhabdomyolysis, or withdrawal of therapy compared with placebo (4). However, the authors notified that further study is necessary to determine whether the results from published clinical trials are similar to what occurs in routine practice, particularly among patients who are older, have more severe comorbid conditions, or receive higher statin doses than most patients in trials they analyzed for the review. In fact, Bruckert et al. had earlier published a large-scale, comprehensive investigation of risk, cause, nature and management of muscle symptoms in patients receiving high-dose statin therapy in clinical practice (5). One of the important observations of this PRIMO-study was that the frequency of mild and moderate muscle symptoms with high dose statin therapy might be more common and exert a greater impact on everyday life than previously thought. In the PRIMO study population (n=7,924 patients receiving high dose statin treatment), 10.5% of the patients on high dose statin therapy complained of muscle pain, while the highest rate (18.2%) was associated with high dose simvastatin treatment. Thus, well-defined arguments can be stated to support muscle safety of statins, but also to demonstrate a common harmful impact on everyday life.

A number of smaller studies have focused to evaluate the mechanisms of possible statin effects in muscle. Phillips et al. have shown that some patients who develop muscle symptoms while receiving statin therapy have demonstrable weakness and histopathologic findings of myopathy despite normal serum creatine kinase (CK) levels (6). Furthermore, we have observed significant changes in skeletal muscle cholesterol metabolism and respiratory chain enzyme activity in asymptomatic patients on high dose statin treatment without elevated serum CK levels (7). Based on these observations it seems likely that significant alterations may occur in muscle metabolism in patients on statins without significant changes in the CK levels. A lack of reliable biomarker makes it difficult to interpret clinical study results on statin safety based mainly on CK measurements. Better biomarkers would also help physicians to decide whether patients' muscle complains without evidential CK elevation necessitate any changes in their lipid-lowering treatment. To study more closely metabolic effects in muscle during high dose statin treatment, we performed bioinformatics analysis of whole genome expression profiling of muscle specimens and UPLC/MS based lipidomics analyses of plasma samples obtained in the above mentioned randomized trial from patients either on high dose simvastatin (80 mg), atorvastatin (40 mg), or placebo (7). We recorded 111 differentially expressed genes (1.5-fold change and p-value < 0.05) in the high dose simvastatin group, while expression of only one and five genes was altered in the placebo and atorvastatin groups, respectively (8). The Gene Set Enrichment Analysis identified 23 affected pathways (False Discovery

Rate q-value < 0.1) in muscle following high dose simvastatin, including eicosanoid synthesis and phospholipase C pathways. We also found that the plasma lipidomic changes following simvastatin treatment correlate with the muscle expression of the arachidonate 5-lipoxygenase-activating protein. Our results demonstrated that high dose simvastatin affects multiple metabolic and signalling pathways in skeletal muscle, which may lead to unexpected metabolic effects in non-hepatic tissues. Intriguingly, the plasma lipidomic profile may serve as a highly sensitive biomarker of statin-induced metabolic alterations in muscle and may thus allow us to identify patients who should be treated with a lower dose to prevent a possible toxicity.

The exact mechanism of statin-induced myopathy is still unclear. We do know rather well that some diseases such as hypothyroidism, liver dysfunction and diabetes are increasing the risk of muscle complications of statin treatment. Exercise, alcohol or infections may also increase the risk. Some patients are obviously having a higher systemic bioavailability for statins possibly due to numerous drug interactions or due to some unknown (possibly genetic) factors in the metabolism of different statins. Another option could be a pre-existing molecular or metabolic defect. Troseid et al. have described four related patients with statin-associated muscle symptoms and normal creatine kinase levels (9). In their patients, two (mother and son) had pathological myopathy related findings on EMG and muscle biopsies also showed evidence of mitochondrial pathology. A third patient (daughter) had slight myopathic findings on EMG and muscle biopsy. In a fourth patient, there were no pathological findings. The authors concluded that an inherited vulnerability, possibly a mitochondrial pathology, might cause or aggravate symptoms in some statin-treated patients. As well, in the PRIMO study family history of muscular symptoms with or without lipid-lowering therapy appeared as a significant predictor of statin related muscle pain in a multivariate model. Thus, a genetic predisposition may play a significant role in the development of statin related muscle symptoms.

To study whether statin treatment could aggregate pre-existing mitochondrial pathologies we determined whether muscle mitochondrial DNA (mtDNA) levels are altered during statin therapy and, therefore, quantified mt-DNA in 86 skeletal muscle biopsy specimens collected as part of a previously mentioned clinical trial of high-dose simvastatin or atorvastatin versus placebo (10). We determined mtDNA/nuclear DNA (nDNA) ratio in muscle biopsies collected before and after 8 weeks of treatment with placebo (n=14), high-dose atorvastatin 40 mg/day (n=15), or high dose simvastatin 80 mg/day (n=14). At baseline, mtDNA/nDNA ratios were not different between the three treatment groups, however a significant decrease (-47%) in muscle mtDNA levels was observed in the simvastatin group between baseline and the 8-week follow-up (Fig.). Indeed, 7/14 patients in the simvastatin group showed a greater than 50% decrease in mtDNA at follow-up, whereas only 2/15 and 0/14 such decreases occurred in the atorvastatin and placebo groups, respectively.

This finding was in accordance with muscle mitochondrial respiratory chain-enzyme complex activity assays in selected participants suggesting decreased total mitochondrial volume or fewer mitochondria per cell in the simvastatin group. The selective elimination of mitochondria, including mtDNA, has been described in apoptotic cells (11) and in cells exposed to inhibitors of mitochondrial function (12). Our results suggest that statin therapy can be associated with mtDNA depletion, probably caused by the treatment itself. It is possible that in our patients, high-dose simvastatin treatment induced stress on skeletal myocytes that led to the elimination of mitochondria and reduced levels of mtDNA. Drawing a parallel with metabolic mitochondrial diseases, such mtDNA depletion

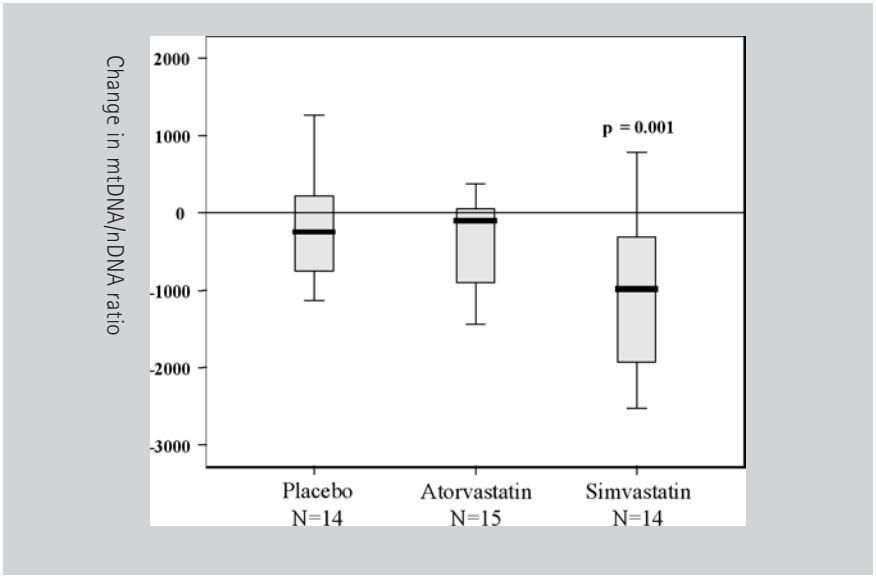

Figure. *Changes in mtDNA/nDNA ratio after 8 weeks of high-dose statin treatment.*

may contribute to mitochondrial dysfunction and play a role in statin induced myopathy. A key feature of this study was that no subjects reported muscle weakness or pain or showed elevated serum CK at follow-up, despite significant decreases in muscle mtDNA in those treated with simvastatin. This would be consistent with the ''threshold effect" observed in mtDNA-depletion disease, whereby clinical muscle symptoms appear only after mtDNA levels fall below 25–30% of normal. The observations herein obviously spark interest in measuring muscle mtDNA levels in patients who experience myopathy while on statin therapy, especially in the light of the magnitude of the mtDNA decrease observed here over a very short period of asymptomatic statin treatment.

Mukhtar and Reckless have listed four potential statin myopathy mechanisms in their recent review: Depletion of intracellular cholesterol leading to calcium influx; inhibited protein synthesis, signal transduction and metabolism due to decreased mevalonate acid and its metabolite concentrations; reduced ubiquinone (coenzyme Q10) concentrations; and enhanced apoptosis (13). Expression of genes related to cholesterol metabolism or mevalonate pathway was only modestly affected by statins in our study. Thus, our present data do not directly support the view that statins would cause mitochondrial dysfunction by reducing ubiquinone, a mitochondrial coenzyme with a cholesterol synthetic pathway derived side chain, due to inhibition of HMG-CoA reductase in the muscle. Similarly we were not able to provide evidence that statins would lead to inhibition of protein synthesis, signal transduction and metabolism due to decreased muscle mevalonate acid. Since our patients did not have any signs of clinical myopathy and muscle damage, we were not able to judge the significance of early proapoptotic markers during the course of the myopathy. However, in the GSEA analysis several pro-apoptosis pathways already appeared with significant FDR q-values at these early stages and, therefore, the present results support the role of proapoptosis pathways in statin myotoxicity. Furthermore, the hypothesis of an increased Ca^{2+} influx as a mediator of statin induced toxicity is supported by the significant up-regulation of phospholipase C pathway and by the dysregulation of genes encoding for calcium binding proteins in our study. Another hallmark of high dose simvastatin effect in muscle was the activation of pro-inflammatory pathways such as eicosanoid synthesis. However, our results cannot reveal the actual trigger leading to impaired mitochondrial function and induction of these proinflamatory pathways. A similar gene expression experiment was also performed on healthy volunteers by Urso et al. (14). They observed only little effect on gene expression at rest due to 4-week atorvastatin (80 mg/d) treatment similar to our results. However, when combined with exercise, 56 genes were expressed differently with 18% involved in the ubiquitine-proteasome pathway. In addition, 20% of the affected genes were related to protein folding, catabolism and apoptosis.

Based on our data at the doses studied as well as clinical reports mentioned above, simvastatin and atorvastatin seem to differ in their effect on muscle metabolism. However, the specific properties of these drugs that lead to different effects on muscle mitochondria are unknown. Despite the risk of myopathy, which appears increased in individuals with an underlying genetic susceptibility for metabolic myopathies (9,15), statin therapy is clearly beneficial to the majority of hypercholesterolemic patients at risk for cardiovascular disease. However, the results of this study reinforce the need to closely monitor closely patients receiving statin therapy, especially those on high-dose, and to identify a sensitive and reliable clinical marker of statin toxicity. Recently, the *United States' National Lipid Association's Muscle Safety Expert Panel* has pointed out the need for a validated measuring instrument for statin-related muscle complaints as existing methods may lack sensitivity and specificity. Our combined transcriptomic and lipidomic analysis provides bona fide sensitive biomarkers of statin induced metabolic changes in muscle potentially useful to identify patients at risk early enough to prevent actual muscle damage. These biomarkers are now available for further validation in patients with proven statin-induced myopathy.

Literature: See page 15.

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Adverse drug reactions of statins

Until the end of December 2006, the Finnish National ADR Register received 513 reports in which statins were considered as suspect medication for the ADR. Majority of the reports included well-known adverse reactions of statins such as musculoskeletal, hepatobiliary, and gastrointestinal disorders. Serious cases are rare and mostly associated with high dose statin therapy and interactions.

HMG CoA reductase inhibitors, statins are originally fungal metabolites, and the earliest statin, compactin, was discovered from *Penicillium citrinum* in the mid 1970s. Statins lower serum cholesterol levels by inhibiting cholesterol synthesis which in turn increases hepatic low density lipoprotein (LDL) receptor expression and the clearance of atherogenic LDL. Large randomised clinical trials have convincingly shown that effective serum cholesterol reduction with statins decrease significantly coronary mortality in primary and especially secondary prevention. Due to intensive therapy to achieve these goals the potential for increased risk of ADRs with such therapy increase.

The well known adverse drug reactions related to statins therapy include hepatobiliary, musculoskeletal, and gastrointestinal disorders. Rare adverse effects include rash, chronic fatigue, hypersensitivity and neuropathy. Memory loss, sleeping disorders and malignancies have also been reported. Some, like rhabdomyolysis and liver failure, can be fatal. In 2002, marketing authorisation of cerivastatin was withdrawn because of concerns regarding an increased risk of rhabdomyolysis.

Statins are authorised in Finland since 1988. At present, six statins, atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin are available in the Finnish market. Number of generic products are increasing continuously and there are 12 generic products of lovastatin, 22 generic products of pravastatin, and 28 generic products of simvastatin.According to the wholesale consumption of statins in Finland 2006, simvastatin is widely used, followed by atorvastatin.

During 1988–2006, the Finnish ADR Register received 513 reports in which statins were considered as suspect medications for the ADR (Table 1). A total of 857 ADRs were reported, and 141 cases were considered as serious. Majority of the reports were received of atorvastatin, followed of simvastatin, fluvastatin, rosuvastatin, lovastatin and pravastatin. The causal relationship with statins is not established with all reported ADRs. Cases in which statins were reported as concomitant medication are not discussed here.

Common ADRs

As expected, musculoskeletal, hepatobiliary, skin and gastrointestinal ADRs were frequently reported for each statin (Table 1). Of the 215 ADRs of myalgia and/or CK increased, 56 reactions were associated with simvastatin, 27 with lovastatin, 9 with pravastatin, 34 with fluvastatin, 44 with atorvastatin, and 45 with rosuvastatin. In a suspicion of myopathy during statin therapy, serum CK level should be measured and if it exceeds 5 fold maximum reference value the therapy should be discontinued.

Uncommon ADRs

Sleep disorders, insomnia, parasomnia, memory loss, micturition disorders, erectile dysfunction, depression, and malignancies have also been reported in patients taking statins. Some of the SPCs contain these adverse effects in the section 4.8. Whether these ADRs are likely to be class effects have been discussed in PhVWP of EMEA. Atorvastatin was associated with increased risk of haemorrhagic stroke in a recent published SPARCLE study. In a published PROSPER study, pravastatin was associated with new malignancies, although the latter was not associated with simvastatin during 10-years follow up in Scandinavian 4S study. In our national register, one case of prostate cancer was identified in a patient with atorvastatin therapy. Another 59 years old male patient experienced recurrent liposarcoma and leiomyosarcoma after approxymately 1 year treatment with rosuvastatin. The nervous psychiatric disorders of interest and erectile dysfunctions are presented in Table 2.

Hypersensitivity

Drug-induced hypersensitivity reactions are immunologically mediated and statins have been associated infrequently with a variety of these reactions. Generally urticaria, angioedema and dyspnaea are the most frequent symptoms of hypersensitivity. In Finnish National ADR register, in

Table 1. *Most frequently reported adverse drug reactions (ADRs) according to System organ classification (SOC]*

Drug	Number of reports **	No of serious cases	No of ADRs	System organ classification (SOC) term (4 most common) , (incl. laboratory terms)	No of ADRs
Simvastatin	123	33	212	Musculoskeletal	87
				Skin and subcutaneous tissue disorders	36
				Hepatobiliary	23
				General disorders and admi nis tration site condition	15
Lovastatin	64	9	105	Musculoskeletal	36
				Hepatobiliary	16
				Psychiatric disorders	15
				Gastrointestinal	10
Pravastatin	24	7	37	Musculoskeletal	21
				Hepatobiliary	8
				Psychiatric disorders	3
				Eye and ear	3
Fluvastatin	94	28*	172	Musculoskeletal	50
				Hepatobiliary	43
				Gastrointestinal	24
				General disorders and administration site condition	10
Atorvastatin	131	44*	205	Musculoskeletal	63
				Hepatobiliary	36
				Skin and subcutaneous tissue disorders	30
				Nervous disorders	19
Serivastatin	7	1	10	Different SOCs	10
Rosuvastatin	75	19*	116	Musculoskeletal	55
				Hepatobiliary	15
				Skin and subcutaneous tissue disorders	11
				General disorders and administration site condition	9

** Including 1 fatal case.*
*** In few reports more than one statin was suspected.*

Table 3. *Hypersensitivity reactions*

	Atorvastatin	Fluvastatin	Lovastatin	Rosuvastatin	Simvastatin
Urticaria	5	1	1	1	3
Angiooedema	1				
Polymyalgia rheumatica			2	1	
Lupus like reaction			1		1
Photosensitivity reaction	1	2			
Arthralgia	4	6	3	3	6
Arthritis	1	1		1	2
Eosinophilia			1		1
Vasculitis			1		1

Table 2. *Nervous psychiatric disorders and erectile dysfunctions associated with the use of statins.*

Simvastatin	depression	1
	sleep disorders	1
Lovastatin	depression	4
	insomnia	5
	parasomnia	1
	sleep disorders	2
	erectile dysfunction	1
Pravastatin	parasomnia	1
	sleep disorders	1
Fluvastatin	memory loss	1
	insomnia	2
Atorvastatin	insomnia	3
	erectile dysfunction	3
Rosuvastatin	memory loss	1
	insomnia	1

addition to urticaria, arthralgia and arthritis were identified with high frequency for all statins except pravastatin (Table 3). Very few cases of polymyalgia rheumatica were linked to lovastatin and rosuvastatin therapy. With regard to pravastatin only one case of autoimmune haemolytic anaemia was reported. Although hypersensitivity is contraindicated in the SPCs of all statins it is important for healthcare professionals to recognise these manifestations of hypersensitivity because they have been rarely associated with HMG-CoA inhibitors.

Interactions

A total of 8 suspected interactions were reported (Table 4). Rhabdomyolysis was reported in 5 cases and associated with high dose statin therapy. The cytochrome P-450 system is involved in statin metabolism, although its functions differ among statins. Drugs that can inhibit cytochrome P-450-mediated metabolism of statins have potential for clinically significant interaction. Few inhibitors are contraindicated for statin treatment. If a concomitant use is required, it has been suggested that the initiation dose of statin should be minimal and patients should be closely monitored for ADRs

Table 4. *Interactions.*

Patient	Statin	Concomitant medication	ADR	Latency
52-y. M	simvastatin 80 mg/day	ciklosporin	rhabdomyolysis	approx 1 month after ciclosporine
51-y. F	simvastatin 80 mg/day	fluvoxamine	rhabdomyolysis	approx 1 month after simvastatin
85-y. F	simvastatin 80 mg/day	clarithromycin	rhabdomyolysis	approx 1 week after clarithromycin
F	simvastatin 10 mg/day	lercanidipine	alopaecia	approx 1 month after lercanipine
54-y. F	lovastatin 80 mg/day	itraconazol	rhabdomyolysis	approx 2 weeks after itraconazole
45-y. M	fluvastatin 20 mg/day	ethanol	prolonged alkohol effect	
67-y. M	atorvastatin 80 mg/day	gemfibrozil, eplerenone	renal insufficiency, CK increased	after 1 m after increasing eplererone
77-y.	atorvastatin 40 mg/day	fluconazol	rhabdomyolysis	

especially for myopathy.

Due to additive risk, the concurrent use of HMG-CoA reductase inhibitors and fibric acid derivatives has resulted in fulminant rhabdomyolysis as early as three weeks after the initiation of therapy. Ezetimibe may also potentiate myopathy associated with statin therapy. Therefore these combination therapies should be considered only if the potential benefit outweighs the increased risk of adverse effects.

Are the ADRs reversible?

Approxymately 300 patients recovered mostly after discontinuation of statin therapy, and 150 patients have not recovered despite statin withdrawal at the time of the reporting. In 55 ADR reports outcome was not reported. Frequency of recovery from serious ADRs of special interest are provided in the Figure 1. Approximately half of the rhabdomyolysis and pancreatitis cases and majority of the neuropathy and joint related disorders cases did not have favourable outcome at the time of the reporting. One fatal rhabdomyolysis was reported. Most of the ADRs including hepatic enzyme elevation and myopathy are mostly reversible after discontinuation of statins.

Cases with fatal outcome

Since 1973, a total of 630 ADR reports with fatal outcome were received in Finnish ADR register. Among these reports only in 3 reports, statins was suspected to have association with patients' death. A 76-years old patient with concomitant fluconazole, an inhibitor of CYP3A4 experienced progressive myopathy, rhabdomyolysis and renal failure and succumbed to multiorgan failure following the change of pravastatin to atorvastatin. An interaction between fluconazole and atorvastatin was suspected in this case although the patient had history of previous surgery for a ruptured aortic aneurysm followed by rhabdomyolysis and renal insufficiency. Atorvastatin, but not pravastatin undergoes significant CYP3A4-mediated metabolism. In the second case, a 41 years male patient with rosuvastatin 20 mg daily dose and concomitant ezetimibe experienced a sudden death after a cross country walk. No further information was available. In the third case, a 58 years old female patient died due to hepatic cirrhosis and acute liver failure after 4 months treatment with fluvastatin. Fatal rhabdomyolysis and acute liver failure are very rare adverse reactions associated with statin therapy especially in high doses and in the presence of drug interaction.

In summary, HMG-CoA inhibitors are among the most frequently prescribed medications and are generally well tolerated. A few patients experience reversible clinical and biochemical adverse effects including elevation of transaminases or creatine kinase or myopathy. Adverse effects occur more frequently with the use of the higher doses and in the presence of other drugs (eg. ciclosporin, erythromycin, ketoconazole, fibrates or ezetimibe). Dose titration is advocated. Awareness of the ADRs and clinically significant interaction among clinicians continues to be important, and counceling patients on possible adverse effects is recommended. By reporting rare ADRs, the safety profile of statins still can be expanded.

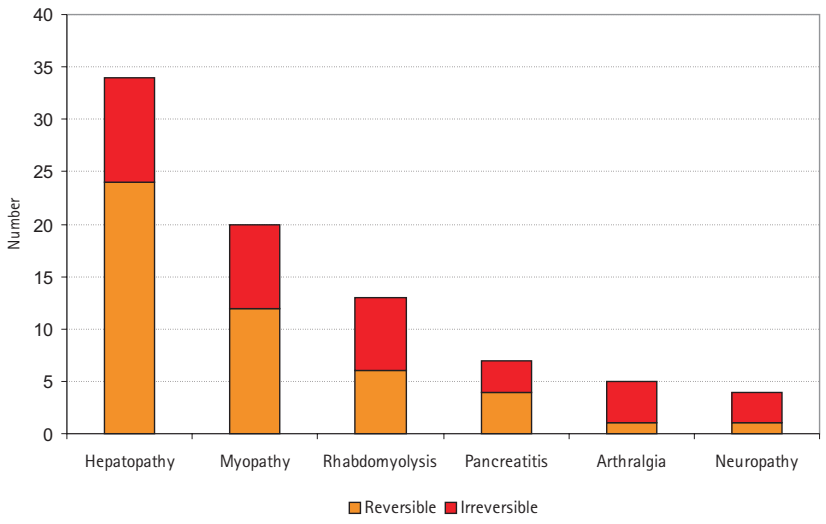

Fig. *Recovery from serious ADRs of interest*

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Own observation of an adverse reaction

Memory disturbance caused by statins

A male born in 1945, with academic education and a managerial position, was admitted for consultation with an internal medicine specialist due to high blood pressure in August 2004. He was bodily obese in spite of active exercise (even running marathons) and the correct constituents of his diet. Anti-hypertensive treatment was initiated with ramipril 10 mg, with lerkanidipine 10 mg and acetylsalicylic acid 100 mg added to the treatment on 12.11.2004. Hypertension was subsequently adequately controlled and the patient's condition was good. Full control of the risk factors, however, was not achieved with non-pharmaceutical measures as the patient's cholesterol levels remained high albeit reduced: 7.2–5.7 mmol/l, LDL cholesterol 4.5–3.4 mmol/l, HDL cholesterol 2.2–1.9 mmol/l, triglyceride 1.1–1.0 mmol/l. Rosuvastatin 10 mg was added as an adjunct to the therapy on 2.12.2004.

Initially the patient could not observe any adverse effects of the medication given, but after three months, in March 2005, he started suffering from significant memory impairment. He began to forget the names of his colleagues, which resulted in embarrassing situations.

According to the standards at the time, a good lipid level was achieved on 23.3.2005: cholesterol 5.0 mmol/l, LDL cholesterol 2.2 mmol/l, HDL cholesterol 2.5 mmol/l, triglyceride 0.6 mmol/l. The patient subsequently stopped taking rosuvastatin of his own accord on 5.4.2005 and noticed on 30.5.2005 that his memory was restored to normal. He was aiming at an ideal outcome of treatment and so spontaneously resumed the treatment with rosuvastatin on 1.9.2005. This led in consequence to a distinctly reduced memory function by as early as 10.9.2005. He then started taking a dose of 10 mg on alternate days, and eventually withdrew from rosuvastatin therapy altogether.

The case was thought to be possibly of a drug-specific character, and the water soluble rosuvastatin was therefore replaced by fluvastatin in a depot formula 80 mg x 1 on 29.9.2005. Following three months' therapy he again noticed distinct impairment of his memory and the drug was this time replaced by ezetimib 10 mg, introduced on 1.12.2005. After half a year's therapy with ezetimib he has no longer suffered from memory impairment and the lipid profile on 4.4.2006 was excellent: cholesterol 4.1 mmol/l, LDL cholesterol 1.7 mmol/l, HDL cholesterol 2.1 mmol/l, triglyceride 0.6 mmol/l, and the conclusion is that the memory disturbance is not associated with the levels of the lipids.

Follow-up studies have indicated a reduced risk of dementia in patients on statins. On the one hand, the protection mechanism is thought to be provided by inhibition of amyloid production and consequently inhibited plaque formation in the brain (1). There are, on the other hand, reports of statin-induced memory disturbances with the suggested mechanism being the inhibition of myelin production, which leads to the demyelinisation of neurofibrils (2). Further studies have not, however, been able unequivocally to prove beneficial anti-amyloid effects (3). Patients on statins generally suffer from cardiovascular diseases and associated cerebrovascular accidents, which may be confusing when looking into the causes of memory disturbances. Our patient, who had suffered the adverse reaction, is showing no signs of cerebrovascular accidents.

It is a question of a very rare adverse reaction. The most extensive review found in the literature concerns 60 patients. About one third of the memory disturbances were cases of sudden loss of memory of the transient global amnesia type, and two thirds were non-specific memory disturbances (3). The median time period between the initiation of medication and realisation of a memory disturbance was 60 days. Memory disturbances have been reported in association with the use of at least the following statins: simvastatin, lovastatin, fluvastatin, pravastatin, cerivastatin and rosuvastatin (4, 5). This rare adverse reaction does not have a great significance in prescribing when treating the large group of high risk patients, but it should be borne in mind in individual cases where adverse reactions occur.

Literature: See page 20.

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Own observation of an adverse reaction

Disulfiram and liver effects

Disulfiram has already for a long time been in use in the withdrawal treatment of alcoholism, administered both in tablet form and, previously, as implants. Its use has somewhat increased in recent years, and last year it was used daily by about 4 400 persons. There is definitive proof of the efficacy of disulfiram when it is used under supervision and when the medication is accompanied by supportive treatments. The drug is without effect when it is used unsupervised.

Safety

Disulfiram apparently also inhibits several liver enzymes including the CYP2E1 enzyme. In addition to pharmacokinetic interactions, it has been found for example to possess a hypotensive effect, and while it interacts with drugs having a cardiac and cardiovascular effect it apparently also causes confusion in concomitant use with antidepressants.

Disulfiram is known to have occasioned encephalopathy, in which case the symptoms may look like psychiatric symptoms; furthermore, psychoses, confusion, sleep disturbances, hallucinations, depression and anxiety have generally been occasioned in users. Peripheral neuropathy has occurred as well as other neurological symptoms (optic neuritis, headache, vertigo, ataxia and spasms); rash has also been reported.

Liver function disorders have been the most common adverse reactions reported to the National Agency for Medicines. A total of 34 adverse reactions were reported, 24 of which involved liver function: in nine cases elevated liver values were reported, 12 cases involved hepatitis, and two of these were presumed to have been fatal. Two reports of liver necrosis have been received. Up until April this year, as many as four reports had been received of severe liver effects in patients who had been on disulfiram therapy.

The instructions in the summary of product characteristics must be followed

The adverse effects and conditions for effective use of the drug have been presented in the SPC for disulfiram. The therapeutic indications state that the product is used as a supportive therapy adjunct to other forms of treatment in alcoholics seeking care.

Specific instructions for follow-up have been given for the prophylaxis of liver effects. The transaminases, serum GT and bilirubin should be assessed before the introduction of pharmaceutical therapy and at 2-week intervals for the following two months, followed by the monitoring of liver values at 3–6-week intervals.

Since proof of benefit is available only from supervised use in conjunction with other supportive measures, and because the adverse effects may be life threatening, restrictions suggested for the use of disulfiram should be taken literally. Adverse liver effects ought to be actively suspected and liver values should be checked.

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Use of biological antirheumatic drugs in Finland in 2005

The biological antirheumatic agents constitute the most recent advances in the treatment of rheumatoid arthritis and other rheumatic diseases. Biological antirheumatic agents are used in the treatment of patients who have not responded to treatment with conventional antirheumatic agents. Due to the high costs and potential of severe adverse effects, however, the use of biological agents has thus far been limited to relatively few patients.

Biological antirheumatic agents are protein macromolecules produced in cell cultures and intended for the treatment of rheumatic diseases. The biological agents can delay or even arrest the slow progression of cartilage destruction and eventual joint damage typical of rheumatoid joint inflammation. They can also alleviate symptoms in such rheumatic diseases which do not respond to conventional disease-modifying antirheumatic drugs.

Four biological antirheumatic agents were on the Finnish market in 2005. Of these agents, infliximab is not included in the drug refund system, because it is used in the form of an infusion administered to a patient in hospital, whereas etanercept, adalimumab and anakinra are given to the patient in the form of injections. The latter belong to the group of drugs with limited basic reimbursability, since they are very costly and the extensive therapy is targeted to patients most likely to benefit from them. Even though the use of biological antirheumatic agents has so far been limited to a few thousands of patients, in 2005 the costs of the reimbursed biological antirheumatic agents already amounted to over 70% of the total antirheumatic drug costs refunded by the *Social Insurance Institution* (SII) (1).

This study investigated the costs and consumption of biological antirheumatic medicinal products in 2005 by using the refund entitlement database and the drug purchase records of the SII. From the records of the SII a 90% sample was taken of the individuals who had a valid entitlement to a restricted basic reimbursement for their biological antirheumatic agents for the entire year. The requested data did not include information on the disease diagnosis or severity. The subject material consisted of 1,417 individuals, i.e. 71% of those who had received a refund for the cost of their biological antirheumatic agents in 2005. The material covered 71% of the total out-patient consumption of etanercept and adalimumab, and 77% of that of anakinra.

Results

The vast majority (84%) of the users of reimbursed biological antirheumatic agents were 15 to 64 years of age. The median age of men was 47 years and of women 49 years. The proportion of retired people among the 15 to 64-year-olds was 38%, which reflects the degree of severity of the disease, as the corresponding proportion in the general population was 13%.

Etanercept was purchased by 889 of the subjects (63%), adalimumab by 627 (44%) and anakinra by 45 (3%). The majority (1,275, i.e. 90%) had used only one reimbursed biological antirheumatic agent during the year, whereas 140 individuals (10%) had used two and only two individuals had used three. Of those who had used only one agent, 755 (59%) had used etanercept, 497 (39%) adalimumab and 23 anakinra (2%). The total consumption of reimbursed biological antirheumatics was on average 297 DDD (median 328 DDD) per person. The consumption among men was on average 300 DDD and women 295 DDD. The average consumption of etanercept per person per year was 267 DDD, adalimumab 279 DDD and anakinra 186 DDD. The difference between the sexes was statistically significant only in the consumption of etanercept, which was an average of 18 DDD higher in men compared with women. The average annual consumption of etanercept per child among the under 15-year-olds was 248 DDD (n=77) and of adalimumab 243 DDD (n=16).

Among the subjects, 70% had also used some conventional disease-modifying antirheumatic drug, and 59% had used a systemic glucocorticoid; 45% had used drugs from both categories mentioned above, 15% from neither of them. Systemic glucocorticoids had been used by 40% of

the under 25-year-olds, 57% of the 25 to 54-year-olds and 71% of 55-year-olds and over. Three quarters had also used analgesics with basic refund entitlement. The most common analgesics were non-steroidal anti-inflammatory analgesics (M01A), used by 71% of the subjects. The most common of those, ibuprofen, had been used by one in four subjects.

The annual cost of reimbursed biological antirheumatic drugs was on average EUR 15,800 per year (median EUR 16,900). The average annual cost of etanercept was EUR 14,300 (median EUR 15,300), of adalimumab EUR 15,000 (median EUR 16,300) and of anakinra EUR 6,800 (median EUR 6,100). The refunds paid out by the SII on average covered 96% of the costs. The average cost of the conventional antirheumatics was EUR 321, and the total costs of antirheumatics were on average EUR 16,100.

Discussion

The clinical response to biological antirheumatics is rapid, often occurring within a couple of weeks from the introduction of the treatment. In accordance with the Finnish Current Care Guidelines (2), the response to a biological antirheumatic drug should be assessed after three months of treatment by using the ACR50 criteria set by the American College of Rheumatology. If no response is obtained, therapy should be changed. As a rule, biological antirheumatics are used as courses of treatment, i.e. until the rheumatic disease is alleviated. States of remission are commonplace in rheumatic diseases, and the situation may in fact be controlled for a longer period of time, but continuous drug treatment is typically required to maintain remission.

During the year of survey, 140 subjects used more than one biological antirheumatic agent, which is likely to have been an indication of a change of the prescribed drug. Replacing one biological medicinal product with another may be due to poor or impaired efficacy of the first drug or to the adverse reactions it had caused. Adverse effects caused by biological medicinal products include allergic reactions and exposure of the patient to infections. Symptom-free tuberculosis in particular may become activated during immunosuppressive treatment (2).

In accordance with the Finnish Current Care Guidelines for rheumatoid arthritis (2), biological antirheumatic therapies should mainly be given in combination with methotrexate. In practice this was adhered to in less than half the survey subjects. However, methotrexate is not appropriate for all patients, and the study included also patients with other rheumatic diseases than rheumatoid arthritis.

A systemic glucocorticoid was combined with biological products in children less often than in adults, which was probably due to the possibility that a systemic glucocorticoid may slow down growth in the children. Overall, the use of systemic glucocorticoids has been found to be more common in those who have suffered from rheumatoid arthritis for a longer period of time (3).

Active treatment with biological antirheumatics is very expensive – a three-month course of treatment costs about EUR 5,000 – but at its best also very effective. In a recently published meta-analysis (4) adalimumab, etanercept and infliximab were found to be effective antirheumatics in patients in who had not satisfactorily responded to conventional treatment. Etanercept was shown to be the most cost-effective (4). A recent Finnish report (5) on overall costs of rheumatoid arthritis estimated that the majority of the costs incurred by society consisted of indirect costs in the form of sickness leaves, disability pensions and lost productivity. According to the reported estimates, the indirect costs would be even higher than at present without the development during the past two decades of such treatment methods which inhibit and delay the progression of rheumatoid arthritis. The industrial engineering study was not yet able to assess the effect of biological antirheumatic drugs, but once they have become common enough, a similar survey is recommended to balance the increasing costs of antirheumatic agents against the cost savings to society.

Biosimilars?

In recent years, substantial savings have been achieved in drug costs with the aid of generic drugs, to which abbreviated marketing authorisation procedures are applicable. Due to the complexity of biological drugs, however, the generic approach is not adequate for the regulatory approval of the so called biosimilars (Similar Biological Medicinal Products). A phenomenon similar to the cost reduction of small-molecule drugs is therefore not to be expected with the biological antirheumatic agents within the near future. Increasing competition and the development of production technologies can nevertheless be expected to lead to improved cost efficiency and, eventually, to reduced prices for biological antirheumatic agents.

Literature: see page 48.