April 2017 Volume 3

MED CHECK

-The Informed Prescriber

№ 7

Anti PD-1 antibody: pembrolizumab

Effective only for non-small cell lung cancer of specific type

New Cholesterol Lowering Agents (PCSK9 Inhibitors)

Infection and neurological diseases increase

CONTENTS （April 2017, Vol. 3, No. 7）

MED CHECK -The Informed Prescriber

Editorial

Time to wake up from a nightmare
— "cholesterol=devil" hypothesis

Translated from the Editorial in Med Check-TIP (in Japanese) Jan 2017 : 17 (69)

Keywords:
overall survival, cholesterol hypothesis, PCSK9inhibitor, CETP inhibitor, familial hypercholesterolemia

Interventions, including those with medicines, are not useful even if a medical complication is related with some risk factors (e.g. remarkable hypertension and hyperglycemia), and those factors are mitigated by the intervention. It must be demonstrated by long-term randomized controlled studies that the intervention can reduce complications and improve survival.

However, it seems that the mainstream of the medical world is going in a totally different direction. Prevention of cardiovascular diseases by medical treatment based on the "cholesterol hypothesis" is one of the typical cases. We dare to say "cholesterol=devil hypothesis" instead of "cholesterol hypothesis" because the mainstream medical researchers and practitioners are trying to remove cholesterol totally as if it is a devil.

Contrarily, cholesterol is never a devil but an essential substance for the body. It has become well known that people with higher total cholesterol may live longer. Many epidemiologic surveys also reported recently that people with higher LDL cholesterol level may live longer. A systematic review which was published in June 2016 revealed that people aged 60 years and older with higher LDL cholesterol lived longer almost without exception (abstract on p10). It was the article which was read most frequently for five months following the month of the publication on the BMJ Open Journal. It shows that the public has high interest in this issue.

On the other hand, scholars insisting on the "cholesterol=devil" hypothesis counterattack fiercely against this article. The prime example is the joint guideline by the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS). The guideline recommend that in people at very high cardiovascular risk, LDL-cholesterol should be lowered to <1.8 mmol/L (70 mg/dL), or in people whose baseline cholesterol level is between 1.8 and 3.5 mmol/L (70-135 mg/dL), it should be lowered at least by 50% .

Cholesterol lowering agents with new mechanisms of action, including PCSK9 inhibitors (p10) and CETP inhibitors (p10), have been developed and many are still underway to be developed. The idea of "Cholesterol= devil" is growing more aggressive as to support the development of the new agents. In clinical trials, such as those on evolocumab, LDL -cholesterol levels decreased by 30-40% , and in many cases they decreased to 25 mg/dL or lower. These data may mislead clinicians to believe that the lower, the better.

The main reason why people with familial hypercholesterolemia (FH) are prone to have myocardial infarction is not because of their high cholesterol level. The real reason is that they also have a genetic disposition to induce high level of inflammatory cytokine, including TNF-alfa, which easily causes inflammation. This predisposition is also the factor that prevents people with FH from being infected with various pathogens, and that is why they lived longer than non-FH people when infectious diseases were the main cause of death.

Is it worth to spend approximately 23,000-70,000 yen (200-600US $)/2 weeks or 0.3-1.8 million yen (5,000-16,000 US $) per year for the agents whose harm outweighs the benefit?

Now is the time to wake up from the nightmare of the "cholesterol=devil" hypothesis, otherwise terrible unwanted events may occur.

Anti PD-1 antibody: pembrolizumab (brand name: Keytruda)

Effective only for non-small cell lung cancer of specific type

Translated from Med Check-TIP (in Japanese) Mar. 2017 ; 17 (70):32-34

Abstract

Pembrolizumab, a class drug of nivolumab, prolongs progression free survival (PFS) and overall survival (OS) in patients who had previously untreated advanced NSCLC with PD-L1 expression on at least 50% of tumor cells. In patients whose PD-L1 expression level was below 50%, the agent also disrupts function of PD-L1 on normal immune cells and may suppress immunity, causing cancer progression, increased infection and autoimmune diseases.

The use of pembrolizumab should be restricted to patients with PD-L1 expression level of 50% or higher, in both previously treated and untreated patients. For previously treated patients whose PD-L1 expression level is below 50%, more detailed study is needed. Because the effectiveness of nivolumab has not been proven in patients with PD-L1 expression level of 50% or higher, it should be not used as a first-line treatment.

Keywords:
anti PD-1 antibody, pembrolizumab, PD-L1 expression level, immune disorders, overall survival, progression free survival

Introduction

Anti PD-1 antibodies such as nivolumab (brand name: Opdivo) bind to Programmed cell Death-1 (PD-1) and preserve the function of this protein. PD-1 is essential for normal functioning of T-lymphocytes, which attack cancer cells and viral-infected cells. Although their effect as an immunity booster has been highlighted, they disrupt the function of PD-L1 on normal immune cells and suppress immunity. As a result, they may allow cancer progression, increase infection and induce autoimmune diseases. This was emphasized in the Med Check-TIP No. 66**[1]**.

Opdivo did not succeed as a first-line treatment of non-small cell lung cancer with a PD-L1 expression level of 5% or higher. However, pembrolizumab (brand name: Keytruda) yielded a positive result as a first-line treatment of non-small cell lung cancer with a PD-L1 expression level of 50% of higher**[4]**. This means that theory that had been asserted in the Med Check-TIP No. 66 was confirmed. This article examines the differences between these 2 drugs.

Trial for a first-line treatment with nivolumab

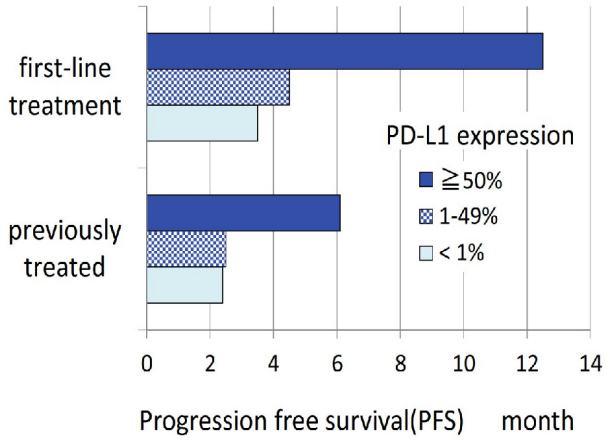
In a trial in which nivolumab was used as a first-line treatment for non-small cell lung cancer with a PD-L1 expression level of 5% or higher, the median progression free survival (PFS) was 4.2 months in a nivolumab group and 5.9 months in a chemotherapy group. Compared to the chemotherapy, nivolumab did not demonstrate superiority, but it was even inferior. The hazard ratio (HR) for progression/death was 1.15 (95%CI: 0.91-1.45, p=0.25). The HR for death was reported to be 1.02 (0.80-1.30) **[2, 3]**. Nivolumab should not be used as a first-line treatment.

The phase I trial on pembrolizumab

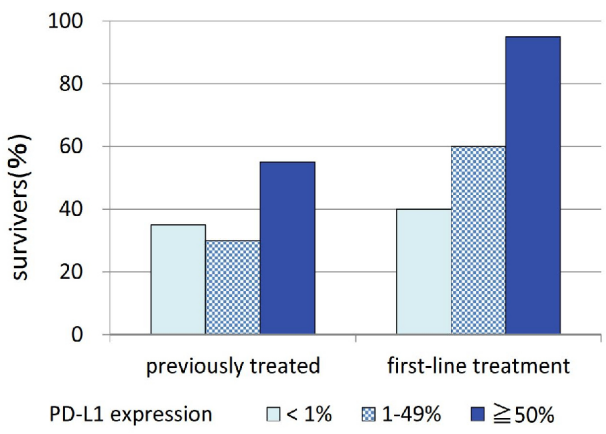
In prior to the phase III trial **[4]**, a large-scale phase I trial was conducted on pembrolizumab **[5]** which was different from ordinary phase I trial. The study enrolled 495 non-small cell lung cancer patients who were classified into 3 groups according to their PD-L1 expression levels. It compared the effect of pembrolizumab on patients who received it as a first-line treatment and those who had been treated previously. No difference was observed in patients with PD-L1 expression level of below 1% and 1%-49%, and positive result was yielded in patients with PD-L1 expression level of 50% or higher even as a first-line treatment (**Figure 1a, 1b**). For instance, as a first-line treatment, PFS (**Figure 1a**) was 12.5 months in patients with high PD-L1 expression level, which

Figure 1: Result of the pembrolizumab phase I trial

a)Median progression free survival (PFS)

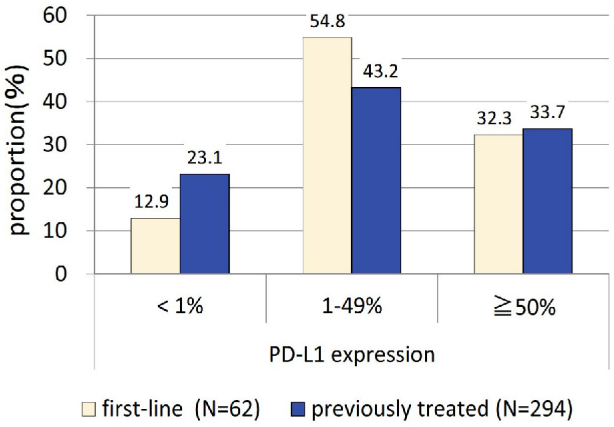


b)Overall survival at 15 weeks (%)



Apart from PD-L1 expression level (%) and the number of initially/previously treated patients, these values were taken mainly from the graphs. In both PFS and OS, patients with PD-L1 expression level of 50% or higher demonstrated extremely more positive outcome, compared with those whose PD-L1 expression level was below 50%. Pembrolizumab was administered at 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, or 10 mg/kg every 2 weeks, but no difference was found among these dosage groups.

c)PD-L1 expression



Whether the patients had been previously treated or untreated did not affect much the proportion of non-small cell lung cancer patients whose PD-L1 expression level was 50% or higher. At least, a single use of chemotherapeutic agents does not seem to raise PD-L1 expression level. However, it remains unknown for patients at the terminal stage.

was more than 2-fold of that in patients with low PD-L1 expression level. Overall survival (OS) (%) at 15 months was 95% in patients who was treated initially (40%-60% in patients with a low PD-L1 expression level) and 55% in previously treated patients (30%-35% in patients with a low PD-L1 expression level), showing marked improvement (**Figure 1b**).

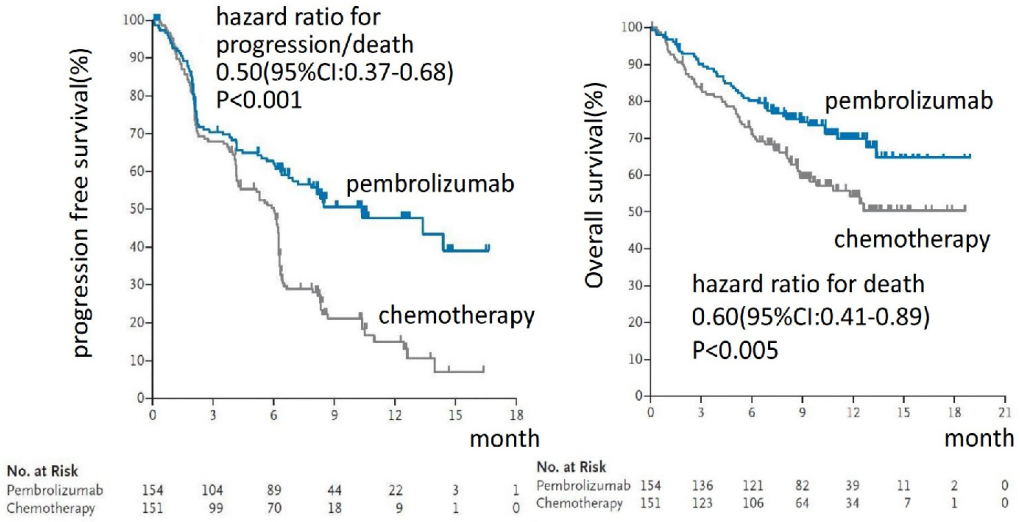
The dosages of pembrolizumab were 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, and 10 mg/kg every 2 weeks. No difference was reported by dosage **[5]**.

The proportion of patients with PD-L1 expression level of 50% or higher was approximately 30% in both previously untreated and treated groups (**Figure 1c**). This indicates that chemotherapy does not affect PD-L1 expression so much.

The phase II/III trial for previously treated non-small cell lung cancer

The phase II/III trial for non-small cell lung cancer was an open label trial that enrolled 1034 previously treated patients. In the trial, 2 dosages of pembrolizumab (2 mg/

Figure 2: KEYNOTE-024 (initial treatment for non-small cell lung cancer)



kg, 10 mg/kg) every 3 weeks and docetaxel 75 mg/m2 every 3 weeks were administered and compared **[6]**.

Almost no difference was found between the 2 dosages of pembrolizumab in any outcomes. However, in patients with PD-L1 expression level of 50% or higher, they showed marked difference, compared with the docetaxel group.

Then, the results from the 2 dosage groups were combined and compared with that from the docetaxel group. The HR for death was 0.53 (95%CI: 0.40-0.70), and HR for progression/death was 0.59 (95%CI: 0.46-0.74), and they both improved markedly. In patients with PD-L1 expression level of 1%-49%, OS extended significantly (0.76, 95%CI: 0.60-0.96), but no difference was found in PFS (1.04, 95%CI: 0.85-1.27). More detailed analysis is needed to determine the PD-L1 expression level below 50% at which both OS and PFS improve in previously treated patients.

Table: summary of adverse events in KEYNOTE-024

	Pembrolizumab		Chemotherapy	
	Number	%	Number	%
Adverse events (AE)	113	73.4	135	90.0
Serious AE	33	21.4	31	20.7
Serious AE (≧Grade 3)	29	18.8	29	19.3
Neutropenia (≧Grade 3)	0	0.0	20	13.3
vomiting	4	2.6	30	20.0
Vomiting (≧Grade 3)	1	0.6	1	0.7
Immune-mediated: any	45	29.2	7	4.7
Immune-mediated (≧Grade 3)	15	9.7	1	0.7
Hypothyroidism/hyperthyroidism	26	16.9	4	2.7
Severe skin reaction(≧Grade 3)	6	3.9	0	0.0
Pneumonitis	9	5.8	1	0.7
Colitis (≧Grade 3)	2	1.3	0	0.0

Immune-mediated disorders of Grade 3 or higher occurred only in 1 patient (pneumonitis) in the chemotherapy group while in the pembrolizumab group, drug eruption (6 patients), pneumonitis (4), colitis (2), hypophysitis (1), nephritis (1), pancreatitis (1), and type 1 diabetes (1) were reported.

KEYNOTE-024: a trial with untreated patients

A phase III trial was conducted to determine the effectiveness of pembrolizumab as a first-line treatment, assigning 305 patients who had previously untreated advanced NSCLC with PD-L1 expression on at least 50% of tumor cells and no sensitizing mutation of the epidermal growth factor receptor (EGFR) gene or translocation of the ALK (anaplastic lymphoma kinase) gene.

In a pembrolizumab group, a fixed dose of 200 mg was administered every 3 weeks, and in a control group, platinum-containing chemotherapeutic agents were administered (the type of the agents used was decided by investigators). It was an open label comparative study.

When disease progression was observed, it was allowed to replace the chemotherapeutic agents with pembrolizumab.

The primary endpoint was progression free survival (PFS), and the secondary endpoints were overall survival (OS), response rate (RR), and safety (adverse events). Among the patients with advanced lung cancer, in those with PD-L1 expression level of 50% or higher, hazard ratio (HR) for aggravation/death was 0.50 (95%CI: 0.37-0.68, p<0.001), and HR for all deaths was 0.60 (95%CI: 0.41-0.89, p<0.005) (**Figure 2**).

More serious adverse events with pembrolizumab?

Overall, a fewer number of adverse events was reported with pembrolizumab, but there was no difference in serious adverse events. Although neutropenia is serious, it is just transient. In the pembrolizumab group, immunological adverse events occurred significantly more frequently, and those of grade 3 or higher occurred in 15 patients (9.7%), 16 cases while they occurred in 1 patient (0.7%) in a chemotherapy group (**Table**). They included severe drug eruptions, pneumonitis, and colitis. These might persist until death, and the frequency of the events alone is not sufficient for evaluation of this issue.

In practice

When pembrolizumab is used in patients whose PD-L1 expression level is below 50%, the elderly patients, or patients with EGFR gene mutation or ALK translocation, most of whom have a low PD-L1 expression level, it inhibits PD-L1 on normal immune cells, antigen presenting cells (APCs), suppresses immunity, allows cancer progression, and increase infection. In addition, by disrupting the function of PD-L1 on regulatory T cells, it induces autoimmune diseases.

Anti PD-1 antibodies do not demonstrate its benefit in patients with a low PD-L1 expression level with 10% or lower.

The effect of pembrolizumab for previously treated NSCLC should be reanalyzed in patients whose PD-L1 expression level is lower than 50% to establish more restricted indication. The same applies to nivolumab.

by the Med Check -TIP Editorial Team

References

1) Med Check-TIP Editorial team. New anticancer drug Nivolumab (brand name: Opdivo), MedCheckTIP (English); 2016: 2(6): 29-35.

2) ESMO 2016 Press Release: Greater Patient Selection May be Needed for First Line Nivolumab to Improve Progression-free Survival in Advanced Lung Cancer
http://www.esmo.org/Conferences/ESMO-2016-Congress/Press-Media/Greater-Patient-Selection-May-be-Needed-for-First-Line-Nivolumab-to-Improve-Progression-free-Survival-in-Advanced-Lung-Cancer

3) Bristol-Myers Squibb Presents Results From CheckMate -026, a Phase 3 Study of Opdivo (nivolumab) Monotherapy Versus Chemotherapy as First-Line Therapy in a Broad PD-L1 Positive Population With Advanced Lung Cancer: https://www.ono.co.jp/eng/news/pdf/sm_cn161011_3.pdf

4) Reck M et al (KEYNOTE-024 Investigators). Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-33.

5) Garon EB et al (KEYNOTE-001 Investigators) Pembrolizumab for the treatment of non-small cell lung cancer. N Engl J Med. 2015;372(21):2018-28.

6) Herbst RS et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016:387(10027):1540-50.

New Products

New Cholesterol Lowering Agents (PCSK9 Inhibitors)

Infection and neurological diseases increase

Translated from Med Check-TIP (in Japanese) Jan. 2017 ; 17 (1):8-9

Abstract

Cholesterol lowering agents, evolocumab and alirocumab were launched in April and August, 2016, respectively. Evolocumab and alirocumab are monoclonal antibodies targeting at PCSK9, an enzyme that decomposes LDL receptors in hepatocytes. They are believed to increase LDL receptors and lower LDL-cholesterol level. They are injected subcutaneously once every 2 or 4 weeks.

Only short-term clinical trials are available on these agents with the longest trial that lasted only about 1.5 years. No evidence suggests that the agents reduce the incidence of cardiovascular diseases and overall mortality. However, they increase the incidence of infection, and cause serious neurologic diseases and impairment of cognition. These agents are not recommended.

Keywords:

overall survival, PCSK9 inhibitor, evolocumab, alirocumab, neurocognitive disorders, infection, familial hypercholesterolemia

People with higher cholesterol level live longer

Cholesterol, LDL-cholesterol in particular, is an essential substance for the organism. Epidemiological studies **[1-4]** in Japan and overseas have shown that people with higher cholesterol level tend to live longer. Especially, people aged 60 or over with higher cholesterol level live longer almost without exception **[4]**. Therefore, having a high cholesterol level alone does not warrant medical intervention.

PCSK9 inhibitors

PCSK9 is an enzyme which stands for proprotein convertase subtilisin/kexin type 9. PCSK9 inhibitors are recombinant human (IgG2) monoclonal antibodies that bind specifically to this enzyme and inhibit its interaction with low density lipoprotein receptors (LDLRs). The mechanism of action is illustrated in the Figure below **[5]**.

Results from clinical trials for PCSK9 inhibitors

The results from clinical trials for evolocumab (brand name: Repatha) and alirocumab (brand name: Praluent) that were conducted prior to approval are extracted from their respective summary basis of approval (SBA) **[5a, 6a]**, regulatory review reports **[5b, 6b]**, and major papers **[7-11]**, and shown in the Table. Pfizer discontinued all ongoing clinical trials for PCSK9 inhibitors (bococizumab), concluding that it was not likely to provide value to patients, physicians, or shareholders **[12]**.

Randomized placebo-controlled trials (RCTs) were conducted for evolocumab and alirocumab for the maximum duration of 1 year and 1.5 years, respectively. In both trials, the primary outcome was not the prevention of cardiovascular diseases, but merely a lowered LDL cholesterol level at 12 to 52 weeks. The primary outcome of a RCT for alirocumab with a follow-up duration of 1.5 years was also a lowered LDL cholesterol level at 24 weeks.

Only a 1-year RCT for evolocumab suggested decreased cardiovascular events, but it was not a double-blind but open label trial which compared the agent with a standard therapy. Hence the result in favor of evolocumab is not reliable. Furthermore, in this trial, patients were randomly reassigned after completion of 12 RCTs. Patients who had been on evolocumab in the previous trials accounted for approximately two-thirds of the patients in the control group.

Therefore, difference in the incidence of adverse events is less likely to be detected.

Increased infection

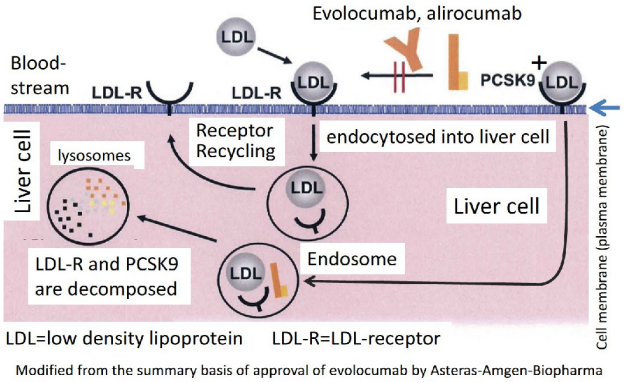
Trials that enrolled patients with familial hypercholesterolemia (FH) showed marked increase of infection **[7, 8]**. In a trial with patients with homozygous FH (HoFH) **[7]**, infection occurred in 6.3% (1/16 cases) with placebo while it occurred in 30.3% (10/33 cases) with evolocumab. The duration of the trial was 12 weeks.

Although the difference was not statistically significant, infection occurred 5 times more frequently in the evolocumab group. (Risk ratio, not odds ratio, is used here as there might be overlap in the number of cases.)

In a trial with patients with heterozygous FH (HeFH) **[8]**, only nasopharyngitis was reported. No other infection was reported in a published paper **[8]** including in its appendix, and SBA. Nasopharyngitis occurred in 5.1% (5/99) in the placebo group and 8.6% (19/220) in the evolocumab group.

The odds ratio was 1.78. Although it was not significant, it was nearly 2-fold higher. Besides infection, high odds ratios were observed in bruising (4.2-fold), back pain (3.7-fold), and nausea (3.7-fold). In a placebo controlled trial enrolling patients with high cholesterol (HC) level **[9]**, many types of infection was reported more frequently in evolocumab group, including upper respiratory tract infection (6.3% vs 9.3%, OR:1.54). In total, they occurred in 41% (125/302) of the patients on placebo and 52.6% (315/599) of the patients

Figure 1: The mechanisms of LDL-cholesterol lowering by PCSK9 inhibitors



Modified from the summary basis of approval of evolocumab by Asteras-Amgen-Biopharma

When LDL-cholesterol binds to its receptors (LDL receptors), it is usually endocytosed into the liver cells. When LDL receptors bind to PCSK9, they are decomposed in lysosomes and are not recycled. Anti PCSK9 monoclonal antibodies (evolocumab, alirocumab) prevent PCSK9 from binding to LDL receptors, suppressing the decomposition of LDL receptors. Undecomposed LDL receptors are recycled, increasing LDL receptors on cell surface. Consequently, increased LDL-cholesterol is endocytosed into the liver cells, and LDL-cholesterol level is lowered **[5]**.

Table: Summary of the phase 2/3 Clinical trial of anti-PCSK9 antibody (As of Dec 2016)

Phase 3 trial [reference No]	Subjects	Control	duration	Primary endpoint	participants (N)		cardiovascular events	All-cause death
					control	exp.	(PL vs anti-PCSK9 ab)	(PL vs anti-PCSK9 ab)
Evolocumab								
Raal 2015[7]	HoFH	Placebo	12w	12w LDL-C	16	33	—	—
Raal 2015[8]	HeFH	Placebo	12w	12w LDL-C	99	220	0% vs 1.5% NS	—
Blom 2015[9]	HC	Placebo	1 year	52w LDL-C	302	599	0.7% vs 1.0% NS	0% vs 0.3% NS
Sabatine2015[10]	various	standard*a	1 year	AE	1489	2976	2.18% vs 0.95% S*b	0.41vs 0.14% NS
Alirocumab								
Japan[6]	HC	Placebo	24w	24w LDL-C	72	143	—	—
Robinson2015[11]	HC	Placebo	1.5 year	24w LDL-C	788	1550	5.1% vs 4.6% NS	—
Including outside Japan[6]	incl. FH	Placebo	≦1.5 y	various	1276	2476	—	—
Outside Japan total [6]		PL/ezetimib	≦1.5 y	various	1792	3182	2.8 vs 3.2% py NS	0.9 vs 0.6% NS

FH: Familial hypercholesterolemia、Ho: Homozygote、He: Heterozygote、HC: Hypercholesterolemia、PL: placebo
AE: adverse events、 py: person-year、NS: not significant, S: significant
*a：open study. The subjects were randomly reassigned to standard treatment (ST) group or ST + evolocumab group, after the completion of total 12 phase 2/3 trials. Consequently, those who were allocated to the placebo group among those who had been in the evolocumab group in the parent trial may be influenced by the adverse effect of evolocumab. No difference was reported for infection. However, among the adverse events, significant difference was found in impairment of cognition (OR:3.4), fatigue (OR:2.8), extremity pain (OR:1.6), joint pain (OR:1.45), headache (OR:1.7), and nausea (OR:1.8).
*b: As this was an open trial, the favorable result for evolocumab is not reliable.

on evolocumab. The risk ratio was 1.16 (95%CI: 1.06-1.28, p=0.0019), and the difference was significant. In an open trial on evolocumab **[10]**, the risk ratio was 1.06 (95%CI: 1.01-1.11, p=0.016). When the 3 placebo controlled trials on evolocumab are combined, the risk ratio for infection is 1.31 (95%CI: 1.13-1.53, p=0.0005).

In a Japanese clinical trial on alirocumab **[6]**, the incidence of infection was 25% (18/72 patients) with placebo while it was 36.4% (52/143 patients) with alirocumab. The odds ratio was 1.71 (p=0.093) and was nearly significant. As for alirocumab, increased infection was not reported in a published RCT **[11]**, but the data suggested the tendency toward increase when all overseas trials included in the SBA were combined.

The combined results of these 5 RCTs and one combined data for alirocumab showed significant risk ratio (RR=1.15, 95%CI: 1.03-1.29, p=0.017).

Serious concern over harm to the central nervous system

Neurological adverse events reported in a placebo controlled RCT **[11]** on alirocumab are important. In alirocumab group, ataxia, demyelination, dysarthria, Miller Fisher syndrome (**note**), and optic neuritis occurred in 1 patient each (no overlap). In other words, total 5 patients (0.32%) reportedly experienced neurological serious adverse events (SAEs). On the other hand, in a placebo group, 2 cases of a neurological SAE were reported, and it was hypoesthesia.

Although no significant difference was observed in frequency (0.32% vs 0.25%), seriousness of the events should be taken into consideration. It is questionable whether hypoesthesia alone can be considered as a serious event. A typical example of central demyelinating diseases is multiple sclerosis. Optic neuritis is also a serious symptom that may be an initial sign that might develop to multiple sclerosis.

According to the summary of overseas placebo RCTs on alirocumab **[6]** (pivotal RCT is reported as reference 11), optic nerve damage occurred in 0.2% (3 patients) with placebo and 0.7% (17 patients) with alirocumab, and the odds ratio was 2.9, which was almost statistically significant (p=0.072). Guillain-Barre syndrome (GBS) occurred in 3.1% (39 patients) with placebo and 3.2% (78 patients) with alirocumab.

Although the difference is not significant, the incidence is extremely high in both groups. It is not clear what unserious GBS is like, but this shows that the substantial number of cases were reported.

An open trial on evolocumab **[10]** reported a significantly higher incidence of neurocognitive adverse events in the study group (0.3% vs 0.9%, OR3.4, p=0.015).

Note: Miller Fisher syndrome is a subtype of Guillain-Barre syndrome (GBS). In most cases, following upper respiratory tract infection, extraocular muscle palsies, ataxia and loss of tendon reflexes acutely progress over 1 to 2 weeks and paralysis in the legs, a typical form which GBS begins with, is absent, and then they naturally improve **[13]**.

Injury adverse events such as bruising occurred frequently.

In the Japanese clinical trial on alirocumab, injury adverse events such as falls and fracture occurred in 1 patient (1.4%) with placebo while they occurred in 17 patients (12%) with alirocumab. The odds ratio was 9.6 (p=0.009). In the placebo group, the patient had only wound, but in the treatment group, they experienced falls (6 patients), fracture (5 patients), bruising (6 patients) and traffic accidents (2 patients). Lack of attention may be a cause of all these events. Increased injuries and increased neurological adverse events share the same root cause.

In a trial on evolocumab enrolling patients with HeFH, only 1 case (1%) of bruising was reported with placebo while 9 cases were reported with the evolocumab (p=0.18).

In practice

PCSK9 inhibitors markedly lower LDL-cholesterol level, but their harm outweighs their benefit. They especially cause increased infection as well as impairment in cognition and neurological function, which is probably associated with increased injuries due to accidents. Having a high cholesterol level is not a sickness, and does not warrant medical intervention at first place. Even in patients with FH, harm of cholesterol lowering agents outweighs their benefit.

For more information, refer to the Med Check-TIP No. 67 **[14]**.

by the Med Check -TIP Editorial Team

References

1) Japan Society for Lipid Nutrition、Guideline: Cholesterol for long life 2010

2) Japan Society for Lipid Nutrition、Guideline 2nd: Cholesterol for long life 2014

3) Hamazaki T, Okuyama H, Ogushi Y, Hama R. Towards a Paradigm Shift in Cholesterol Treatment. A Re-examination of the Cholesterol Issue in Japan. Ann Nutr Metab. 2015;66 Suppl 4:1-116. Free https://www.karger.com/Article/Abstract/381654

4) Ravnskov U, Diamond DM, Hama R, Hamazaki T, Ogushi Y, Okuyama H et al. Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review. BMJ Open. 2016 Jun 12;6(6):e010401 Free https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4908872/pdf/bmjopen-2015-010401.pdf

5) Evolocumab a)Summary Basis of approval,b)Review report by PMDA

6) Alirocumab a)Summary Basis of approval,b)Review report by PMDA

7) Raal FJ, Honarpour N, Blom DJ et al(TESLA Investigators). Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;385(9965):341-50. https://www.ncbi.nlm.nih.gov/pubmed/25282520

8) Raal FJ, Stein EA, Dufour R, et al (RUTHERFORD-2 Investigators) PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet. 2015; 385(9965):331-40. https://www.ncbi.nlm.nih.gov/pubmed/25282519

9) Blom DJ, Hala T, Bolognese M et al(DESCARTES Investigators) A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med. 2014;370(19): 1809-19 https://www.ncbi.nlm.nih.gov/pubmed/24678979

10) Sabatine MS, Giugliano RP, Wiviott SD, et al (OSLER Investigators) Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372(16):1500-9. https://www.ncbi.nlm.nih.gov/pubmed/25773607

11) Robinson JG, Farnier M, Krempf M et al (ODYSSEY LONG TERM Investigators) Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372(16):1489-99. https://www.ncbi.nlm.nih.gov/pubmed/25773378

12) Pfizer: Pfizer Discontinues Global Development of Bococizumab, Its Investigational PCSK9 Inhibitor http://www.pfizer.com/news/press-release/press-release-detail/pfizer_discontinues_global_development_of_bococizumab_its_investigational_pcsk9_inhibitor

13) Japanese Society of Neurology,Practice Guidelines for Guillain-Barré Syndrome and Fisher Syndrome 2013 https://www.neurology-jp.org/guidelinem/gbs.html

14) Hama R. On the treatment for Familial Hypercholesterolemia. MedCheckTIP 2016: 16(6): 122-3.

Top 1 most read for 5 month: paper on cholesterol

Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review: Ravnskov U, Diamond DM, Hama R, Hamazaki T, Ogushi Y, Okuyama H et al. BMJ Open 2016;6:e010401
http://bmjopen.bmj.com/content/6/6/e010401

This was the top 1 most read paper for 5 months from June to October 2016 and has been the top 2 most read for 4 months thereafter in the BMJ Open.
http://blogs.bmj.com/bmjopen/

Abstract

Objective It is well known that total cholesterol becomes less of a risk factor or not at all for all-cause and cardiovascular (CV) mortality with increasing age, but as little is known as to whether low-density lipoprotein cholesterol (LDL-C), one component of total cholesterol, is associated with mortality in the elderly, we decided to investigate this issue.

Setting, participants and outcome measures We sought PubMed for cohort studies, where LDL-C had been investigated as a risk factor for all-cause and/or CV mortality in individuals ≥60 years from the general population.

Results We identified 19 cohort studies including 30 cohorts with a total of 68 094 elderly people, where all-cause mortality was recorded in 28 cohorts and CV mortality in 9 cohorts. Inverse association between all-cause mortality and LDL-C was seen in 16 cohorts (in 14 with statistical significance) representing 92 % of the number of participants, where this association was recorded. In the rest, no association was found. In two cohorts, CV mortality was highest in the lowest LDL-C quartile and with statistical significance; in seven cohorts, no association was found.

Conclusions High LDL-C is inversely associated with mortality in most people over 60 years. This finding is inconsistent with the cholesterol hypothesis (ie, that cholesterol, particularly LDL-C, is inherently atherogenic). Since elderly people with high LDL-C live as long or longer than those with low LDL-C, our analysis provides reason to question the validity of the cholesterol hypothesis. Moreover, our study provides the rationale for a re-evaluation of guidelines recommending pharmacological reduction of LDL-C in the elderly as a component of cardiovascular disease prevention strategies (see also Editorial: p2.)

RCTs of cholesterol lowering agents of different classes were cancelled in succession

Lilly announced in October 2015 that they had discontinued development of evacetrapib, a cholesterol lowering agent [1].It is an inhibitor of cholesteryl ester transfer protein (CETP). The phase 3 trial had been conducted worldwide including in Japan. However, Lilly accepted the recommendation of the independent data monitoring committee to terminate the Phase 3 trial due to insufficient efficacy of the agent (a low probability the study would achieve its primary endpoint) [1].

CETP transfers cholesterol ester of HDL-cholesterol to LDL. When CETP is inhibited, LDL-cholesterol decreases and HDL-cholesterol increases. Because of this clear theoretical basis, these agents were expected to achieve a large market share, following statin. The major pharmaceutical companies competed for development of this class agent. However, evacetrapib has become the third CETP inhibitor whose development was cancelled after reaching phase 3, the final stage of the development.

Torcetrapib (Pfizer) was the first CETP inhibitor halted. All 6 phase 3 RCTs were stopped and development was discontinued in 2006 when it was revealed that all-cause mortality increased by 60 % in the group receiving a combination of torcetrapib and atorvastatin compared with atorvastatin alone [2].Development of dalcetrapib was also canceled because it significantly increased CRP and blood pressure compared with placebo, and was not expected to improve cardiovascular events [3]. The third case is evacetrapib. Lilly commented the study was cancelled not because of safety reason [1]. It seems there was no difference in cardiovascular events [4]. However, no detailed adverse event data are available yet.

Development of PCSK9 inhibitor was stopped recently. Pfizer discontinued development of bococizumab because it was not likely to provide value to patients, physicians, or shareholders. On November 1, 2016 they announced the discontinuation of two ongoing long-term cardiovascular outcome studies. Pfizer has observed an attenuation of LDL-cholesterol lowering over time, as well as a higher level of immunogenicity (antibody production) and higher rate of injection-site reactions [5]. However, it is unknown whether incidence of infection and neuropathy were frequent like two other PCSK9 inhibitors (cf. p 6~ and Editorial: p2)

References

1) Eli Lilly and Company：
http://lilly.mediaroom.com/index.php?s=9042&item=137476
2) https://en.wikipedia.org/wiki/Torcetrapib
3) Schwartz GG et al. N Engl J Med. 2012:;367(22):2089-99
4) https://en.wikipedia.org/wiki/Evacetrapib
5) Pfizer 2016.11.1
http://www.pfizer.com/news/press-release/press-release-detail/pfizer_discontinues_global_development_of_bococizumab_its_investigational_pcsk9_inhibitor

MED CHECK

The Informed Prescriber
2017 Vol.3 No.7