lipoproteins, lowers LDL-cholesterol on average by 28%. This compound, mipomersen, is injected weekly subcutaneously.

A second agent that inhibits the formation of apoB-containing lipoproteins in liver and gut is an inhibitor of microsomal triglyceride transfer protein (MTP). This compound lowered LDL-cholesterol by 50% in patients with homozygous familial hypercholesterolemia. A side effect of both classes of drugs is the accumulation of fat in the liver.

Proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) is a protease that induces degradation of LDL-receptors. Statins increase the concentration of PCSK9, thereby attenuating their LDL-cholesterol–lowering effect. Combining statins with inhibitors of PCSK9 has proven to be very effective in LDL-cholesterol lowering: injection of monoclonal antibodies to PCSK9 biweekly on top of maximal statin therapy lowered LDL-cholesterol by an extra 60%. If long-term treatment with these antibodies proves to be safe, this will change the treatment of patients with severe familial hypercholesterolemia. The near future years will also provide the final verdict whether raising HDL-cholesterol by means of inhibition of cholesteryl ester transfer protein (CETP) will be of any benefit.

Disclosure of Interest: A. Stalenhoef: consultant for Genzyme.

ANTI-TNF IN OCULAR DISEASES

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Summary: Tumor necrosis factor-alpha (TNF-alpha) plays a role in the process of intraocular inflammation that is the cause that the use of TNF-alpha inhibitor agents is worldwide spread to treat different form of intraocular inflammations. In ophthalmology, anti-TNFs are applied in the treatment of uveitis and immune-vasculitis. The number of TNF-alpha inhibitors is increasing despite the fact that such kind of medication can be used "off-label" in the treatment of inflammations. TNF-alpha inhibitors are effective at first in that form of uveitis that is connected with systemic immunologic diseases: Mo. Behcet, rheumatoid arthritis (especially with juvenile idiopathic arthritis), Mo. Chrohn, Wegener granulomatosis, autoimmune diseases (lupus-like syndrome [LLS]). In cases of vasculitis, it can be used in giant cell arthritis, Takayasu arthritis, primary angiitis of the central nervous system, and Cogan syndrome. Anti–TNF-alpha also are effective in cases of autoimmune, noninfectious diseases of the eye: Mo. Harada, sympathetic ophthalmia. The most frequent anti–TNF-alpha that are used are etanercept, adalimumab, and infliximab. There are 3 other TNF-alpha inhibitors that are less widespread yet: golimumab, certolizumab, and tocilizumab. The advantage of the TNF-alpha inhibitors are that they have fewer side effects as corticosteroids and immunsuppressives but are more effective. Their only disadvantage: they are very expensive.

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NEW TARGETS IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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Summary: With the increasing needs for better outcome, function, and quality of life in arthritides and autoimmune diseases, we have increasing amounts of information on the major pathogenetic pathways underlying rheumatoid arthritis (RA), spondyloarthritides (SpA), lupus, scleroderma, and other rheumatic diseases. After decades of reliance on largely empiric approaches in the therapy of most of these diseases, the introduction of TNF-alpha–blocking agents in the late 1990s revolutionized the therapy of rheumatoid arthritis (RA), other arthritides, and connective tissue diseases. Numerous pathways have been targeted and almost 10 biologics have been registered to treat RA, SpA, and lupus. In addition to anti-TNF biologics, further therapies such as anti–IL-6R, CTLA4-inhibitor, or anti-CD20 agents along with several new experimental approaches have since emerged out of improved understanding of the immunopathogenesis. In addition to biologics, the first small molecular targeted therapies, mostly tyrosine kinase inhibitors, have been developed. Most therapies primarily intended for RA, however, have failed to show or have shown only marginal benefit in other autoimmune rheumatic diseases such as lupus, scleroderma, polymyositis, or vasculitides, all of which continue to have a high unmet medical need. Challenges to identify novel drug candidates and to conduct successful clinical studies for such diseases include the different and highly complex immunopathology as well as clinical trial–related issues (eg, the lack of validated, sensitive, and reliable end points). Recently, promising new therapeutic approaches have emerged. This presentation highlights these advances in autoimmune rheumatic diseases.

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WHAT IS THE ADDITIONAL VALUE OF ELECTRONIC MEDICAL RECORDS FOR DRUG SAFETY SIGNAL DETECTION? THE EXPERIENCE OF EU-ADR PROJECT

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Summary: In the last decades, both regulators and manufacturers have used computerized data-mining techniques on reports of adverse drug reactions from both health care practitioners and consumers to detect drug safety signals, that is, unknown or incompletely documented drug-event associations. The signal detection using data from spontaneous reporting system (SRS) databases is negatively influenced however by under- and selective reporting as well as missing denominators. To overcome some of these shortcomings, in the last 5 years, a number of ongoing international initiatives (Sentinel, Protect, OMOP, EU-ADR) has started to explore longitudinal observational health care data, including electronic health records (EHRs), as an additional source for signal detection. The ultimate goal of the EU-ADR project was to develop an innovative, computerized system for the automatic detection of drug safety signals. Using a database network of 7 databases from 3 countries covering ~30 million European patients, EU-ADR developed new methodologies for signal detection and compared the performance (both in terms of precision and timing) of signal detection using either EHRs or SRS through validation sets. Main findings of the project are that EU-ADR is not powered enough to monitor infrequently used/captured drugs and associations regarding very rare events, while SRS may be more efficient. On the other hand, EU-ADR has the most power for signal detection concerning events with higher incidences rate and not commonly reported to SRS. In this presentation, the overview of methodology and results from EU-ADR will be presented and the potentially additional value of exploring EHRs in the context of pharmacovigilance will be discussed.

STUDYING TERATOGENIC EFFECTS OF MEDICATION USE DURING PREGNANCY: CHALLENGES AND PITFALLS

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Summary: Depending on the data sources used and the types of studies included, 29% to 99% of pregnant women in developed countries take at least 1 prescribed drug. Although some drugs, such as thalidomide and isotretinoin, are classical examples of human teratogens (nongenetic risk factors that cause birth defects), the human teratogenic risks are undetermined for >90% of prescription drug treatments approved for marketing in the United States since 1980. Due to this lack of information, adherence to pharmacologic treatment may be discouraged, which may endanger maternal and fetal health, or women may choose to terminate their wanted pregnancies based on fear of adverse effects. In other pregnancies, fetal development may be disturbed by unknown teratogenic exposures that could have been avoided. Therefore, high-quality human studies focusing on the adverse effects of medication use during pregnancy are urgently needed. However, apart from the general methodologic problems in epidemiologic research, such as confounding, selection and information bias, and limitations in making causal inferences, pharmacoepidemiologic studies focusing on birth defects face some important problems that are unique to this area of research. During this lecture, these problems and some new initiatives in epidemiologic research on adverse effects of medication use during pregnancy will be discussed.

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PREDICTION OF PHARMACOLOGICAL EFFECTS OF CNS-ACTIVE AGENTS DURING EARLY PHASES OF DRUG DEVELOPMENT

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Summary: In the last decades, several drugs for neuropsychiatric indication failed in late stages of development or were withdrawn shortly after launch, including disease-modifying compounds for dementia (eg, the γ-secretase inhibitor tarenflurbil) and innovative drugs for smoking addiction (eg, the CB1-antagonist rimonabant). A few years ago, some of the larger pharmaceutical industries decided that the financial risk of developing drugs for psychiatric indications was too large, and many CNS projects were abandoned. Currently, the industry tries to innovate CNS drug development by investing in partnerships with expert groups and exploring novel science-driven approaches. An essential requirement for a successful drug is that it reaches its therapeutic target in the right concentrations during the correct time period, and that it avoids levels or targets associated with adverse events. In addition, the drug's mechanism of action needs to have a beneficial effect on the pathogenesis or pathophysiology of the disease. Most of these aspects can be accurately determined in healthy subjects, in the earliest phases of drug development. To some extent this also includes indications of therapeutic benefit, because many diseases involve well-known physiological processes that are also measurable in normal subjects, although therapeutic benefit can only be reliably examined in patients. Thus, the predictions of the optimal dosing regimen (or the likeliness of failure) of a new drug in patients can be significantly enhanced by demonstration of optimal pharmacologic activity in every early (and later) study during drug development. This lecture will provide several examples, in which pharmacologic effect measurements were incorporated into "traditional" single and multiple ascending dose studies in Phase I. These instruments include (but are not limited to) validated effect biomark-

ers such as the NeuroCart CNS test battery (pharmacologic activity and beneficial/detrimental effects), PET measurements or continuous CSF-sampling (BBB-penetration), pharmacologic challenge tests (pharmacologic activity) or informative positive controls (benchmarking), and pharmacokinetic/dynamic analysis for data integration. The examples involve innovative compounds such as partial GABA-A-agonists and CB1-antagonists, and the first human studies with a fast-dissociating D2-antagonist and an orexin half-antagonist. In most of these cases, traditional approaches were misleading, but a goal-directed "question-based" application of pharmacologic tools in healthy subjects demonstrated brain penetration and meaningful functional effects (indicative of therapeutic or detrimental activity), which contributed to accurate predictions of therapeutic windows in clinical trials.

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INDUSTRY IS MORE FIT FOR CLINICAL TRIALS THAN ACADEMY

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Summary: Drug R&D is costly, time-consuming, and has a low success rate. The costs exceed 1 billion USD. From the human Phase I trial on, the increase is exponential. In the EU, 60% of clinical trials applied for every year are sponsored by the pharmaceutical industry and 40% by other stakeholders, such as academics. It is no wonder, then, that the EU Clinical Trials Directive 2011/20/EC incented protest mainly from the academic and SME stakeholders. According to the EC, although the Directive brought about important improvements in the safety and ethical soundness of clinical trials and in the reliability of clinical trials data, on the other hand, it led to the fall of the number of applications by 25%. The costs have increased. The staff needs for industry sponsors to handle the clinical trial authorization process have doubled, with SMEs facing an even sharper increase. For noncommercial sponsors, the increase in administrative requirements has led to a 98% increase in administrative costs. Insurance fees have increased by 800% for industry sponsors. Although the EC is now about to ease the burdens, it is clear that significant resources would be required anyhow. The proper and time-conscious conduct of extended, multinational, cross-continental clinical studies requires sufficient high-quality staff, logistics, experience, and knowledge of different regulatory aspects, let alone a sound financial background. This can be handled only by the help of industry resources at the end. Trends and data underpinning this opinion will be demonstrated in the presentation.

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COLLECTION AND IMPACT OF PATIENT REPORTED OUTCOMES

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Summary: The efficacy assessment in clinical studies evaluating drug effects, or more generally disease management, is generally focused on the occurrence of objective clinical or economical outcomes, in line with regulatory guidelines. However, there is growing recognition of the value of capturing wider effects of treatments reported by patients in the form of patient-reported outcomes (PROs). A PRO is defined as any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. After examining the reasons explaining the development of these new clinical research