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Chapter 1 : Biological therapy for inflammatory bowel disease - Wikipedia

Biological therapy involves the use of living organisms, substances derived from living organisms, or laboratory-produced versions of such substances to treat disease. Some biological therapies for cancer stimulate the body's immune system to act against cancer cells. These types of biological.

In the past 20 years, significant progress has been made in better understanding the pathomechanisms of psoriasis. Initially thought to be an epidermal disorder, psoriasis is now considered a chronic T-cell mediated autoimmune disease. Severe adverse events, such as opportunistic infections and tuberculosis, along with antibodies specifically to the TNFalpha drug with loss of efficacy, have been reported. There has been a shift from approaching psoriasis as a primarily T-cell mediated disease to the development of biologic therapies that directly target cytokine signaling or T-cell function. More targeted treatment options with less impact on the immune system and fewer side-effects are desirable. Many new biologic treatments for psoriasis are undergoing clinical trial development with a more focused approach on specific aspects of cytokine signaling because it is a more targeted approach that may offer a better side effect profile than current evidence-based treatment modalities. Understanding the role of cytokines in the pathogenesis of psoriasis has been critical in developing advances in therapeutic options. The IL cytokine is produced by antigen-presenting cells and is required for the activation and survival of Th17 cells. The Th17 and Th22 cells produce IL and IL, respectively, and have a significant impact on the epidermis with the elicitation of addition proinflammatory cytokines, antimicrobial peptides, and growth factors. These three cytokines signal through the same IL receptor complex. Ustekinumab is a human monoclonal antibody that binds to the p40 protein subunit of both IL and IL with high affinity and specificity. Briakinumab clinical trials demonstrated high levels of efficacy as measured by the PASI response at 12 weeks. Biologics targeting IL Ongoing research has indicated that IL is an important factor in the pathogenesis of inflammatory and autoimmune diseases, including psoriasis. These cytokines signal through the IL receptor complex. In a phase II, double-blind, placebo-controlled trial, Ixekizumab demonstrated significant clinical efficacy for chronic moderate-tosevere plaque psoriasis, as well as scalp and nail involvement. At 12 weeks, a greater than 75 percent reduction in PASI score was noted in over 75 percent of patients receiving 25mg, 75mg, and mg, compared to eight percent with the placebo. A PASI reduction of percent was noted in 38 percent receiving 75mg and 39 percent of patients receiving mg. There were no serious adverse events observed in this phase II trial for ixekizumab, but assessment of safety is difficult due to the small number of patients enrolled in the trial patients and short duration 12 weeks. There were no major cardiovascular events, mycobacterial infection, or systemic fungal infections. Of interest, two of patients 1. Neither of the patients had any concurrent infection. The most common adverse events were nasopharyngitis, upper respiratory infection, injection site reaction, and headache. There were significant dose-dependent reductions from baseline in keratinocyte proliferation, epidermal thickness, hyperplasia, dendritic cell and T cell infiltration of the dermis and epidermis, and keratinocyte expression of innate defense peptides at only two weeks. An ablation of the disease-defining mRNA expression profile was noted by two weeks after the first dose. It has been evaluated in preliminary studies with psoriasis. The clinical response was associated with histologic findings of decreased acanthosis and epidermal hyperplasia, along with a reduction in the gene expression of markers of the ILA pathway. There was one serious adverse event noted in the study, which was the worsening of pre-existing congestive heart disease. Fixed regimens of subcutaneously administered secukinumab 75mg every four weeks x 3 or mg every four weeks x 3 demonstrated efficacy in moderate to severe plaque psoriasis after 12 weeks. The PASI 75 response at 12 weeks was The more common side-effects were nasopharyngitis, upper respiratory tract infection, worsening of psoriasis, fatigue, and peripheral edema. Two patients experienced transient decreases in absolute neutrophils. In a phase I, randomized, placebo-controlled trial, subcutaneous and intravenous brodalumab was compared to placebo. Twenty-five patients received a single dose of either AMG at mg subcutaneously SC ,

mg subcutaneously, mg intravenously IV , or placebo. This clinical response was associated with rapid improvement in multiple skin biomarkers. In this small sample, there were no serious adverse events or deaths. Patients were randomized to receive brodalumab administered subcutaneously at 70mg, mg, or mg at day 1 and weeks 1, 2, 4, 6, 8, and 10, or mg monthly, or placebo. At week 12, the median percentage improvement in PASI was There was significant improvement in skin biomarkers measured. There were two cases of grade 3 asymptomatic neutropenia reported in the mg brodalumab group. The interleukin IL is important for Th1 cell differentiation. IL, which is important for Th17 differentiation and survival, has two subunits: By targeting the subunit p19, rather than p40, there is a specific inhibition of IL without blocking IL With preservation of the IL pathway, Th1 stimulation is allowed to continue. Th1 immunity is preserved and risk of side effects may be decreased. The drug was evaluated for safety and tolerability following intravenous or subcutaneous administration in a single ascending dose study. IL regulates the expression of genes which impact cellular differentiation and antimicrobial defense. There is a correlation between IL levels and the severity of the disease. Biologic agents are being developed that directly target cytokine signaling or T-cell function. With a more targeted approach on the immune system, newer biologic agents may have the potential to produce greater efficacy with an improved side effect profile. Most of the newer biologic agents for the treatment of psoriasis are in preliminary phase II clinical trials. The clinical efficacy and potential adverse events of these new agents will be more greatly appreciated as the clinical trials enter phase III studies. At the present time, the small number of patients treated and the short duration of the studies make accurate assessment of efficacy and safety difficult. The future of biologic therapy in the management of psoriasis remains challenging and exciting. Bechtel is on the speakers bureaus for Abbott, Amgen, Janssen. Levinson have no relevant conflicts. Immunopathogenesis and role of T cells in psoriasis. Clin Dermatol ; 25 6: Cytokine-based therapy in psoriasis. Importance in pathogenesis and therapy of psoriasis. Dermatology Online Oct 15; 18 ILA is essential for cell activation and inflammatory gene circuits in subjects with psoriasis. J Allergy Clin Immunol Jul; 1: Novel systemic drugs under investigation for the treatment of psoriasis. J Am Acad Dermatol July; 67 1: Lancet May 17; Arch Dermatol Feb; Anti-cytokine therapies for psoriasis. Exp Cell Res May 15; 9: Characterization of interleukin isoforms and receptors in lesional psoriatic skin. Br J Dermatol Feb; 2: Anti-interleukin monoclonal antibody ixekizumab in chronic plaque psoriasis. N Eng J Med Mar 29; Effects of AIN, a fully human antibody to interleukinA, on psoriasis, rheumatoid arthritis, and uveitis. Sci Transl Med Oct 6; 2 52 52ra Efficacy and safety of secukinumab in the treatment of moderate to severe plaque psoriasis: Br J Dermatol Oct 27 E pub ahead of print. Anti-IL receptor antibody AMG leads to rapid clinical response in subjects with moderate to severe psoriasis: J Invest Dermatol Oct; Brodalumab, an anti-interleukinreceptor antibody for psoriasis. Putting together the psoriasis puzzle. An update on developing targeted therapies. Sofen H, Smith S. Matheson R, et al. Results of a single ascending dose study to assess the safety and tolerability of CNTO following intravenous or subcutaneous administration in healthy subjects and in subjects with moderate to severe psoriasis. Br J Dermatol ; IL regulates the expression of genes responsible for antimicrobial defense, cellular differentiation, and mobility in keratinocytes: Eur J Immunol ;

Chapter 2 : Biologic Therapies in Clinical Development for the Treatment of Rheumatoid Arthritis

The therapeutic objective in patients with rheumatoid arthritis (RA) is reduction of disease activity with an ultimate goal of disease remission. Limitations of currently available disease-modifying antirheumatic drugs and biologic therapies suggest that there remains an unmet need for agents that.

The PASI score rates psoriasis on a scale of 0â€”72 based on the erythema, induration, and scale of the plaques weighted by body surface area, with higher scores representing more severe disease and a PASI score of 12 representing the minimal score to qualify for clinical trials for moderate-to-severe disease. A low PASI score at the end of a study may better represent a good response, however, as patients with a lower score at the beginning of the study may be less likely to reach a PASI Methods The objective of this paper is to provide a concise review of the current biologic therapies for moderate-to-severe plaque psoriasis that target IL and IL A literature review, undertaken by the authors, searched PubMed for articles in English using the following key words: IL, IL, psoriasis, BI, briakinumab, brodalumab, guselkumab, ixekizumab, secukinumab, tildrakizumab, and ustekinumab. Duplicate articles were removed, and article titles were reviewed. Of these, the abstracts for articles were reviewed. Of these, articles were selected for further review. Our paper focuses on the most recent phases of relevant clinical trials. This was not a systematic review, and not all results can be directly compared to each other, due to differing study specifics, methodology, endpoints, and objectives. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors. This approval was expanded in to include the indication psoriatic arthritis [20]. Clinical Trials Based on data from several clinical trials and post-marketing registries, ustekinumab is safe and efficacious in the treatment of moderate-to-severe plaque psoriasis [22 â€” 26]. PASI 75 was achieved in Subjects taking ustekinumab were also more likely to have PGA scores of 0 or 1 at week Efficacy and safety parameters were similar in the two treatment groups [27]. These results were not compared with transitioning to ustekinumab after a washout period. Based on registry data of over 12, patients, ustekinumab does not increase the risk of malignancy, major adverse cardiovascular events MACE , serious infections, or mortality and has been shown by multiple registries BADBIR, Danish, and PSOLAR to be the biologic agent least likely to be discontinued [26 , 30 , 31]. In , after phase III trials, Abbott Laboratories discontinued all clinical trials and withdrew their application for approval after concern of a possible increased risk for MACE, defined as myocardial infarction, cerebrovascular accident, and cardiac death [32]. There are no clinical trials currently ongoing relating to this drug. Clinical Trials Before its development was discontinued, briakinumab showed significant promise in phase III trials [33]. In a randomized, double-blind, placebo-controlled study, Serious infections five versus one event on briakinumab and placebo, respectively , non-melanoma skin cancers ten versus zero events , and MACE seven versus zero events were more common in those on briakinumab than placebo. A statistically significant p value was not reported for any of these data points [33]. When compared to methotrexate, briakinumab was more effective with a faster onset of efficacy [36]. In a week, randomized, double-blind study with a week open-label extension, subjects were randomized 1: At week 24, PASI 75 was achieved in Serious adverse events were reported in 9. It has no affinity for IL Clinical Trials A randomized, double-blind, phase IIb clinical trial revealed that tildrakizumab was effective in treating moderate-to-severe plaque psoriasis. At week 16, the proportion of subjects achieving PASI 75 was significantly higher at all doses when compared to placebo: Tildrakizumab demonstrated a low rate of relapse after cessation of therapy, with only 3. Phase III studies are in progress [38 , 39]. Clinical Trials A phase I, proof-of-concept study of BI demonstrated a similar frequency of side effects with varying doses of BI compared to placebo [40]. The most common side effects were mild-to-moderate upper respiratory infections, mild nasopharyngitis, and mild-to-moderate headache [40]. Phase II trials have been completed, and publication of results is pending. Additional trials are ongoing [41]. Seventy percent of patients treated with adalimumab achieved PASI 75, and the statistical significance of

this compared to guselkumab was not reported [42]. Larger, phase III trials are currently underway [43 â€” 45]. In , it was approved in the US and in Europe as a first line drug for the treatment of moderate-to-severe plaque psoriasis [21 , 47]. In the same study, This study also reported high usability of a prefilled syringe with a safety profile similar to previous studies [49]. A study comparing retreatment-as-needed secukinumab versus fixed-interval secukinumab was unable to show a statistically significant difference between the two dosing methods, although the rates of those achieving and maintaining PASI 75 were numerically higher in the fixed-interval group [50]. The most common side effects associated with this drug are nasopharyngitis, headache, and upper respiratory infections, which are similar to other biologic drugs [46]. The most common adverse events seen in these trials were nasopharyngitis and injection site reactions, with rates and severity comparable to etanercept [52]. Additional studies are ongoing. In May , Amgen announced that it would no longer be co-developing and commercializing brodalumab with AstraZeneca due to concerns over increased suicidal ideation and behavior [54]. Clinical Trials Before Amgen terminated its development and commercialization, brodalumab was undergoing phase III trials for moderate-to-severe plaque psoriasis, as well as clinical trials for psoriatic arthritis and axial spondyloarthritis [54]. Brodalumab showed promising results at 12 and weeks in a phase II, randomized, double-blind, placebo-controlled study with an open-label extension period. A subset analysis of the phase II data revealed similar efficacy and patient reported outcomes despite co-existence of psoriatic arthritis or prior biologic use [57]. Additionally, brodalumab at both doses was numerically superior to ustekinumab in achieving complete clearance PASI , but statistical significance of this difference was not consistently achieved: Conclusions Both IL and IL are promising targets in the treatment of moderate-to-severe plaque psoriasis. Biologic drugs targeting these cytokines and their receptors have proven to be effective and safe in clinical trials and have offered greater efficacy than pre-existing biologics, as evidenced by large proportions of patients achieving not only PASI 75 but also PASI 90 and PASI It is important to be vigilant in following the safety profile of these drugs both in clinical trials and in post-marketing registries to ensure their long-term safety. All named authors meet the International Committee of Medical Journal Editors ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. Campa has no conflicts of interest. Mansouri has received an honorarium and has sat on an advisory board for Celgene. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Compliance with Ethics Guidelines This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors. N Engl J Med. The pathogenesis of psoriasis: Psoriasisâ€”epidemiology and clinical spectrum. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: J Am Acad Dermatol. 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Chapter 3 : A Clinical Development Paradigm for Cancer Vaccines and Related Biologics

Biologic therapies have been developed on the basis of a greater understanding of the immune system and disease pathogenesis. Targeting of a specific molecular pathway to influence disease activity is an attractive approach, aiming to limit the side effects commonly associated with conventional immunomodulation.

Bristol-Myers Squibb, Wallingford, CT View on Journal Site Abstract Therapeutic cancer vaccines are a heterogeneous group of complex biologics with distinctly different clinical characteristics than cytotoxic agents. The current clinical development paradigm used for oncology drug development is based on criteria developed for cytotoxic agents. More flexible and focused developmental guidelines are needed to address the unique characteristics of therapeutic cancer vaccines. Over the course of 1 year, the Cancer Vaccine Clinical Trial Working Group, representing academia and the pharmaceutical and biotechnology industries with participation from the US Food and Drug Administration, defined in a consensus process the cornerstones of a new clinical development paradigm for cancer vaccines and related biologics. Four major topics were addressed: The proposed paradigm suggests therapeutic cancer vaccines to be investigated in 2 general types of clinical studies: Proof-of-principle trials, which introduce a novel cancer vaccine into humans, should include a minimum of 20 or more patients in a homogenous, well-defined population in an adjuvant setting or without rapidly progressive disease in a metastatic setting to allow vaccines adequate time to induce biologic activity and should incorporate immune and molecular markers. Objectives should include initiation of a safety database, determination of dose and schedule, and demonstration of biologic activity as proof-of-principle. Biologic activity is defined as any effect of the vaccine on the target disease or host immune system using biologic markers as study end points, for example, clinical, molecular, or immune response. Immune response is demonstrated if determined in 2 separate, established and reproducible assays at 2 consecutive follow-up time points after the baseline assessment. If proof-of-principle trials show such immune response, or other biologic or clinical activity, efficacy trials may be initiated. If none of these end points is met, the clinical development plan should be reevaluated to decide if further development is warranted. Efficacy trials formally establish clinical benefit either directly or through a surrogate and are encouraged to be randomized studies. This is in contrast to single-arm phase 2 trials used for cytotoxic agents, which often use tumor response rate as the primary end point and historical controls as a comparator. Efficacy trials may use prospectively planned adaptive designs to expand from randomized phase 2 into phase 3 studies if well-defined trigger-point criteria are met, but the cost of incorporating such design elements should be carefully evaluated. Efficacy trials can also be exploratory randomized phase 2 trials or conventional phase 3 trials. In addition, conventional clinical end points can be adjusted to account for biologic features of cancer vaccines. The concept of efficacy trials allows for an early assessment of vaccine efficacy based on credible prospective data. This 2-phase developmental paradigm supports a more flexible, expeditious, and focused clinical developmental process with early and informed decision making. In addition, this report addresses clinical development challenges and issues for combination therapies.

Chapter 4 : Biological therapy for cancer - Mayo Clinic

SUPPLEMENT ARTICLE Biologic Therapies in Clinical Development for the Treatment of Rheumatoid Arthritis Mark C. Genovese, MD Abstract: The therapeutic objective in patients with rheumatoid.

Chapter 5 : The Biopharmaceutical Pipeline | PhRMA

Initiation of treatment with DMARDs and Biologics should only be undertaken at a specialist centre within a clinical network, and should always involve a consultant paediatric rheumatologist and a paediatric-trained Clinical Nurse

Specialist (CNS).