A Phase II Study, Evaluating the Efficacy of Montelukast in Reducing the Incidence and Severity of Monoclonal Antibodies Associated Infusion Reactions.

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Synopsis

The use of monoclonal antibodies either alone or as part of chemoimmunotherapy in oncology, benign and malignant hematology is expanding. Each year, United States Food and Drug administration (FDA) approves new agents or expands the indications of already approved agents. Of the 17 therapeutic monoclonal antibodies approved in 2017, 50% of them are indicated for hematologic and oncologic condition. With increasing number of approved agents and expansion of indications of existing agents, therapeutic monoclonal antibodies have become one of the fastest growing areas in the management of benign and malignant hematologic condition. With advancement of recombinant technology, newer agents are either partially or fully humanized. Despite this, they still carry significant risk of immune and non-immune mediated adverse events. Most of the therapeutic monoclonal antibody related adverse events (MCAAE) are either anaphylaxis or standard infusion reactions.

The severity of reaction is variable, ranging from mild involvement of single organ to severe and life-threatening reactions requiring hospitalization or even resulting in death. In a majority of patients, re-initiation of infusion following resolution of symptoms with or without additional medical intervention is possible.

Even for mild infusion reactions, where re-initiation of infusion is possible, there is resultant delay in delivery of infusions, distress to patients, and additional utilization of health care resources.

Due to unpredictability of standard infusion reaction, efforts have been focused on premedication to decreasing the incidence and severity of infusion reaction. Most institutions have protocols using corticosteroid, acetaminophen and antihistamine as part of their premedication protocols. This has reduced but not eliminated standard infusion reactions. Most recently, mast cell stabilizers are being added to standard protocols to further reduce the incidence and severity of standard infusion reactions with variable anecdotal success without formal study. Of all the monoclonal antibodies, only Daratumumab has been evaluated using this strategy.

This study seeks to formally evaluate the efficacy of mast cell stabilizer Montelukast 10 mg (SINGULAIR, Merck & Co., Inc.) in decreasing the standard infusion reaction in patients receiving therapeutic monoclonal antibodies either alone or as part of chemoimmunotherapy in hematologic condition. To our knowledge, this is the first study to formally evaluate this strategy in the multiple monoclonal antibodies. The monoclonal antibodies to be studied include: Blinatumomab (BLINCYTO, Amgen Inc.), Daratumumab (DARZALEX, Janssen Biotech, Inc.), Elotuzumab (EMPLICIT, Bristol-Myers Squibb Company), Gemtuzumab (MYLOTARG, Pfizer Inc.), Obinutuzumab (GAZYVA, Genentech USA, Inc.), and Rituximab (RITUXAN, Genentech US); the most common monoclonal antibodies in hematology associated with high risk of monoclonal antibody associated infusion reaction.

Hypothesis

We postulate that 10 mg of Montelukast, when given at least 1 hour prior to infusion monoclonal antibodies in addition to standard premedication, will lead to at least 50% decrease in incidence of monoclonal antibody associated Standard Infusion Reactions compared to historic data. It will also lead to shorter infusion time and decrease use of additional health care resources (ER, hospitalization and discontinuation of infusion) and hence better tolerability of infusions.

Background/Significance

Immunoglobulin molecules (antibodies) are multifunctional components of immune system produced by B-lymphocytes to facilitate cellular and humoral reaction to host and foreign antigens. Most antibodies are produced, as part of immune response, by diverse clones of B-lymphocytes to antigens. They are polyclonal and target portions of antigens that induced their response. Immunoglobulins can also be monoclonal i.e. produced by single clone of B lymphocyte against a specific antigen.

Monoclonal antibodies are produced commercially using recombinant technologies; they have been available in clinical use since 1985. Since revision of naming convention of therapeutic monoclonal antibodies in 2017, over 500 monoclonal antibodies have been registered(1). In 2017 alone, 17 therapeutic monoclonal antibodies are approved by Food and Drug Administration (FDA), of which 8 are indicated for hematologic and oncologic malignancy(2).

In hematology and oncology, monoclonal antibodies are either used alone or in combination with conventional chemotherapy for management of various benign or malignant conditions. Despite high clinical benefit, their drawback has been their unpredictable adverse effects (infusion reactions). For this reason, newer generations of monoclonal antibodies are either partially or fully humanized. Despite this innovation, their use still carries variable risk of infusion reaction depending on the agent, clinical indication and clinicopathologic characteristic of individual being treated.

Monoclonal antibody associated infusion reactions are generally divided into four general types; type 1 like reaction (most common), cytokine- release syndrome, mixed reaction and type IV reaction (least common) (3). For practical purpose, the above are grouped into anaphylaxis infusion reactions (AIRs) and standard infusion reactions (SIRs).

AIRs are medicated by IgE and result in explosive reaction with initial or subsequent exposure. Re-challenge is generally not recommended.

SIRs are mediated by antigen and antibody interaction (human antihuman or human anti-chimeric) or cytokine released from mast cell and monocyte- macrophage systems. The rate and severity of this type can be mitigated by premedication.

The incidence rates of SIRs are highly variable ranging from 50-80% in Rituximab and Alemtuzumab to 20-30% in Trastuzumab and Cetuximab (4, 5). Incidence is highest with the first and probably the second doses but may recur with subsequent doses in up to 30%(6).

The severities of SIRs are also variable, ranging from mild involvement of single organ to severe reaction resulting in emergency room visit or hospitalization and death. In majority of patients with mild to moderate reactions, re-initiation of therapy with hours to days of break is possible.

Due to unpredictability of SIRs, efforts have been focused on decreasing the incidence and severity of infusion reaction with premedication. Most institutions have adopted various combinations of corticosteroid, acetaminophen and antihistamine as part of their premedication protocols with variable success in reducing the incidence and severity of SIRs.

Despite the above, SIRs still occur with high rates and severities resulting in treatment delays, infusion prolongations, need for additional doses of premedication, emergency room visits and

sometimes hospitalizations. These not only lead to increased cost of treatment but also lasting psychological impact of treatment of patients.

To mitigate the above, efforts are being directed at modifications of premedication or addition of newer agents to further reduce the incidence and severity of SIRs and hence improve tolerability.

Most recently, Montelukast, a mast cell stabilizer has been reported in multiple retrospective and observational studies to either decrease the incidence rate of infusion reactions, shorten infusion time and or decrease the use of additional doses of premedication like corticosteroids whose effect may be counterproductive (7). This has resulted in wide spread use of Montelukast as part of premedication of some monoclonal antibodies without formal study.

Our pilot study seeks to evaluate whether 10 mg of Montelukast, when given at least one hour prior to infusion of monoclonal antibodies with high risk of infusion reaction (Blinatumomab, Daratumumab, Elotuzumab, Gemtuzumab, Obinutuzumab, and Rituximab) will decrease the incidence and severity of infusion reactions, shorten infusion time and improve tolerability. It also seeks to evaluate the frequency of use of extra doses of premedication during the infusion, particularly, corticosteroid whose use is associated with toxicity and is counterproductive to treatment in some situation. This will help identify new regimens to reduce the incidence and severity of SIRs. Information obtained will be hypothesis generating for a future Phase 3 randomized trial with eventual goal of modification of standard of care of monoclonal antibody premedication.

Purpose of the Study

Aim

To evaluate the efficacy of 10 mg of Montelukast in reducing the incidence and severity of monoclonal antibody associated standard infusion reactions (SIRs).

Primary Objective

To report the incidence of monoclonal antibody associated SIRs when 10 mg of Montelukast is added to standard premedication.

Secondary Objectives

1. To report rate of use of extra doses of premedication during infusion of monoclonal antibodies in the cohort
2. To determine the average duration of infusion of above monoclonal antibodies in the cohort

Design of the Study:

This is a Phase II, single arm, open label, clinical trial.

Sample Size:

A total of 100 patients will be screened with anticipated enrollment of 80 into the study. This is based on resources and estimated patients' availability for the study.

Patient Population (Eligibility and Exclusion Criteria):

Consecutive patients who are seen and treated for various hematologic or oncologic malignancies with monoclonal antibodies (Blinatumomab, Daratumumab, Elotuzumab, Gemtuzumab, Obinutuzumab, and Rituximab) in Community Medical Centers- CMC (Community Regional Medical Center (CRMC), and Clovis Community Medical Center (CCMC)) and affiliated Ambulatory Infusion Centers (East Medical Plaza AIC, Clovis Community AIC, and Community Cancer Institute AIC) will be approached for study enrollment. Patients will recruited from CCI, CCMC, and CRMC when they present for evaluation for hematologic or oncologic malignancy by PI or one of the sub-I's. Only patients treated by PI or sub-I's will be recruited into the study. No additional patients from external referral from other hematologist, oncologist, or PCP will be recruited unless they are seen by PI or Sub-I's for treatment evaluation.

Potential subjects will be approached when they present for pre-chemotherapy evaluation for their first dose of chemoimmunotherapy or immunotherapy for above named therapeutic monoclonal antibodies. Subjects who express interest in the study will then be consented for screening, registration and enrollment.

Eligibility Criteria

1. Patients must be at least 18 years.
2. Able to provide consent for study participation (English and Spanish).
3. Patients with hematologic disorders or malignancies starting on any of the following monoclonal antibodies alone or in combination with chemotherapy (Blinatumomab, Daratumumab, Elotuzumab, Gemtuzumab, Obinutuzumab, and Rituximab).
4. Able to tolerate leukotriene antagonist including Montelukast.
5. Able to tolerate oral intake.
6. Available for follow up by phone and on site.

Exclusion Criteria

1. Patients undergoing treatment with above monoclonal antibodies for indications other than stated in above eligibility criteria.
2. Patients who cannot provide informed consent in English or Spanish.
3. Patients taking Montelukast or other leukotriene antagonists for other indications at the time of screening.
4. Known allergic reactions to Montelukast or other leukotriene inhibitors.
5. On monoclonal antibodies other than the ones being studied (Blinatumomab, Daratumumab, Elotuzumab, Gemtuzumab, Obinutuzumab, and Rituximab).
6. History of uncontrolled depression or suicidal ideation or psychiatric illness.

7. Known Severe Hepatic Impairment (AST>10x ULN; ALT>10x ULN; ALP>10x ULN; and/or Bilirubin >5x ULN).
8. Patient with eosinophilic vasculitis.
9. Unable to comply with phone or in person follow-up.
10. Patients participating in another clinical trial.
11. Patients who are pregnant

Study Methods:

Study design:

This is a Phase II single arm open label study evaluating 10 mg Montelukast given at least 1 hour prior to infusion of monoclonal antibody in addition to standard premedication. Monoclonal antibodies being evaluated include those commonly used to treat hematologic and oncologic malignancies like (Blinatumomab, Daratumumab, Elotuzumab, Gemtuzumab, Obinutuzumab, and Rituximab).

The study will be introduced to patients who are undergoing treatment with above monoclonal antibody by principal investigator or sub-investigator during routine pre-initiation of immunotherapy or chemoimmunotherapy visits. Patients who are interested in hearing more about the study will be consented to participate in the study. Subjects will then be screened by study coordinator with the PI or Sub-I and those who are meet inclusion/exclusion criteria will proceed on the study.

Drug for the study will be dispensed by one of the Research pharmacists affiliated to CCI during routine pretreatment evaluation for patient to take home. The study drug (Montelukast) will be purchased from commercial sources using the funds from the study sponsor. This is an investigator-initiated research with full funding from institutional pilot research grant from the Central California Faculty Medical Group (CCFMG). No additional internal or external funding will be utilized for this study.

Study subjects will be given 10 mg of Montelukast to be orally self-administered at least 1 hour prior to beginning of chemotherapy section. The administration of drug by patient will be verified and documented by inpatient or AIC nurse by history.

If the monoclonal antibody is given more than 3 times weekly, then patient will take Montelukast daily, including at least 1 hour prior to infusion or change of bag.

Standard premedication will be administered according to institution protocol. For details, see the flow chart below in appendix 1.

Rates, ratios and proportions with confidence intervals will be calculated for demographic characteristic and incidence of infusion reactions. McNemar's test will be used to test the differences of average incidence of infusion reaction between first and subsequent infusions.

Intervention:
Administration of Montelukast 10 mg at least 1 hour prior to initiation of up to 6 infusion doses/bag changes

Control:
Historic literature and retrospective chart review of patient's treated with above therapeutic monoclonal antibodies from January 2014 to December 2019.

Covariates:
History hypersensitivity medications, history of Asthma or Atopy, history of CAD/COPD, Other chemotherapy received by patient during the infusion and tumor burden.

Study Implementation:
This study is completely voluntary, and enrolment will not affect the treating oncologist's decision or treatment plan. The study medication, Montelukast, is an FDA approved drug for other indications and is not known to pose serious risk to cancer patient undergoing monoclonal antibody or cancer chemotherapy. Patients will be monitored closely for potential drug-drug interactions during the study period.

Information obtained from patients during the study period will be used solely for study purposes. No additional tissues or samples will be obtained for study purpose other than what is collected or required by treating physician as part of standard of care.

Privacy and confidentiality of patients' information will be protected per CMC guidelines.

Participation of study by subject is voluntary and will not require additional visits other than 24-hour post infusion phone call to complete a study related questionnaire. Study subjects will not be reimbursed for participation.

Study will be conducted over 2 years with an estimated yearly accrual of at least 40 patients per year.

The study will be conducted upon approval of CMC Institutional Review Board IRB and will follow Helsinki declaration and Good Clinical Guideline.

Data Collection:

Demographic and clinical data will be collected according to the study plan (Appendix 2). Infusions will be administered per standard of care. The study investigators will obtain information about time of onset, time of completion, types and degree of infusion reaction(s), number of doses of additional medication used to treat infusion reaction and post infusion disposition locations. National Cancer Institute Common Terminology of Standard Adverse Effect (NCI CTCAE v5.0) will be used to grade Infusion-related reactions and Immune system disorder as shown in appendix 4.

Follow up phone calls to patients by study coordinator to ascertain additional reactions and treatments received will be documented. Patients will complete the study on completing 6th dose/bag change of infusion or progression of disease or change of therapy, whichever comes first. For patients on continuous infusion, change of bag will be used as reference point.

Measured Outcomes:

Primary endpoint

1. To estimate the incidence rate of SIRs during above monoclonal antibody infusions.

Secondary endpoints

1. To estimate the average infusion duration of the above monoclonal antibodies
2. To estimate the incidence of Grade 3 or more monoclonal antibody infusion reaction
3. To estimate the rate of discontinuation of monoclonal antibody infusion due to SIRs

Risks of Study Medication:

Risks and side effects related to Singulair include those which are:

Likely adverse reactions (above 5%):

- Upper respiratory infection
- Fever
- Headache
- Pharyngitis (inflammation of the back of the throat)
- Cough
- Abdominal pain
- Diarrhea
- Otitis Media (middle ear infection)
- Influenza
- Rhinorrhea (runny nose)
- Sinusitis (inflammation or swelling of the tissue lining the sinuses)
- Otitis (ear infection)

Less Likely adverse reactions (more than 1% to 5%):

- Fatigue
- Dyspepsia (indigestion)
- Dental pain
- Gastroenteritis (stomach flu)
- Dizziness
- Rash
- Increase in ALT/AST (blood tests evaluating your liver)
- Pyuria (increase in number of white blood cells in the urine)

Very rare but serious adverse reactions (less than 1%):

- Neuropsychiatric events (see below)
- Eosinophilic conditions (see below)

Neuropsychiatric events: Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking Singulair. Post-marketing reports with Singulair use include, but are not limited to, agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia,

irritability, memory impairment, obsessive compulsive symptoms, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tic, and tremor. The clinical details of some post-marketing reports involving Singulair appear consistent with a drug-induced effect.

Eosinophilic conditions: Patients with asthma on therapy with Singulair may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events have been sometimes associated with the reduction of oral corticosteroid therapy.

Other precautions:

- Aspirin sensitivity: Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking Singulair. Although Singulair is effective in improving airway function in asthmatics with documented aspirin sensitivity, it has not been shown to truncate bronchoconstrictor response to aspirin and other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients.
- Phenylketonuria: Phenylketonuria patients should be informed that the 4-mg and 5-mg chewable tablets contain phenylalanine (a component of aspartame), 0.674 and 0.842 mg per 4-mg and 5-mg chewable tablet, respectively.

Statistical Analysis:

Ratios and proportions with confidence intervals will be used to estimate the incidence and grades of infusion reactions. Proportions will also be used to report the use of additional medication during and after monoclonal antibody infusions. McNemar's test will be used to compare the incidence of infusion reaction between first and subsequent infusion.

Data Safety Monitoring and Reporting Plan:

The Primary Investigator or Study Coordinator will monitor the research clinical study in a manner consistent with the applicable health authority regulations and the clinical standards adopted by the investigators.

The scope of the Primary Investigator or designated Study Coordinator's responsibilities include:

- Working with each Investigator and office staff to assure that the protocol, responsibilities and record keeping requirements are understood prior to initiation of the study
- Maintaining close contact with the investigators concerning the progress of the study
- Monitoring the study progress on a regular basis, semi-annually or more frequently
- Handle data entry and/or analysis
- Report Adverse Events in a timely manner

The reporting and monitoring process will be assisted by the following tools:

- A Study Data File for each patient will be created to maintain the information for each patient enrolled in the study. It will include copy of signed/dated Informed Consents and any adverse event reports.
- All submitted clinical data will go through quality assurance review, data entry and statistical analysis.

A Data and Safety Monitor (DSM) will be designated as Team A who will meet with study coordinator and Principal investigator every 4 months or after every 20 patients enrollment and will have access to the de-identified data. The data and safety monitoring team members are not part of study team.

The role of the DSM will be to:

- Evaluate the collected data for participant safety, study conduct and progress
- Make recommendations concerning continuation, modification, or termination of the trial.

The study may be stopped for one or more of the following reasons:

- Study aims are met
- Finding of Unexpected adverse effect related or unrelated to addition of Montelukast to pre-medication protocol
- The DSM determines there are significant safety issues.

Confidentiality and Privacy:

Currently all data for patients who will be starting a treatment regimen that includes monoclonal antibodies either alone or in combination with chemotherapy are kept confidential. Study information for retrospective study will be obtain from EPIC EMR. All information obtained will be confidential and only need to know information will be obtain from EPIC for study purposes only. Both retrospective and prospective information will be stored on password protected, secured online REDCAP database.

Data Security:

All study related charts will be scanned into EPIC and hard copy including consent form will kept securely in the CCI research department in a locked room per CCI research department guidelines.

Study data will be entered into REDCAP database, which is password protected and HIPAA compliant. De-identified password protected data will be downloaded from REDCAP for analysis by research staff. Downloaded data will be stored on password protected CMC/UCSF encrypted computer by PI until at least 1yr post publication after which it will be destroyed per CMC/UCSF protocol. Damages from inadvertent identification of patients and protected patients information will be limited to less than minimum risk by study team.

Adverse Reaction and Adverse Event Reporting:

Throughout the course of the study, all efforts will be made to remain alert to possible adverse experiences or unanticipated findings. If adverse experiences occur, the first concern will be the safety and welfare of the patient, and appropriate medical intervention will be made. Any adverse reactions to the study medication observed by the Investigator or reported by the patient, regardless of severity, will be recorded in the patient's case file and reported to the IRB.

Any patients who are discontinued from the study due to adverse experiences will be followed until their medical outcome is determined, and written reports will be provided to the IRB by the Investigator.

Funding Section:

This study is paid for by a pilot research grant from the Central California Faculty Medical Group (CCFMG). The study doctors and the study staff do not have any financial or non-financial conflicts of interest regarding this study. See Appendix 3 for study budget breakdown.

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