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Mini Review

Rheumatoid Arthritis: Comparative Study of Injections Vs. Acid-Coated Lipid Nanoparticles.

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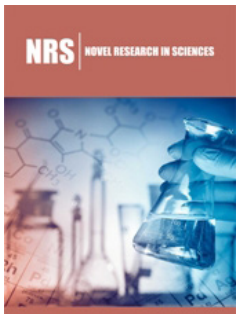

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Introduction

As a formal introduction into the subject matter, there will continually be obligation for drug discovery, synthesis, and intervention. Without such measures, the world will find itself lacking considerably, at it cannot preserve its citizens. In light of recent events in 2020, the coronavirus epidemic has brought to light the disparities in U.S healthcare and the communication deficits it had with the rest of the world. As an underlying problem that the addresses the framework for modern heath, more than ever there is a need to advocate for public health and community health care systems. Whether or not here or in another country, there is much work to be done to ensure our health care system does not fail us again. This program will provide primary experience in order to initiate widespread goals in health care. Advocacy must spread like wild fire in order to bring about the momentary support to fuel clinical trials and drug discovery endeavors. COVID-19 has revealed just how little modern-day science is prepared for novel ailments and diseases that are yet to cause panic. Research is both the heart and brain of discernment. Advocacy is simply acknowledging a problem exists.

Some interesting facts about Learning for Covid-19

COVID-19 brings some precedence to this review paper. The current treatment for the coronavirus, as of 2020, has been z-packs and hydroxychloroquine. The overlap between RA and coronavirus lying in the treatment though the same prescription medication. Both ailments use hydroxychloroquine as a form or relief. Going back to discussion about the novel coronavirus, the FDA approved hydroxychloroquine sulfate as an emergency medication for the treatment of hospitalized COIVID-19 patients. It is significant to note that the FDA fact sheet was dated April third 2020. The fact sheet for health care providers was operating on many unknowns and broad degrees of certainty that hydroxychloroquine sulfate as a course of action would be effective (FDA 2020). More explicitly, the FDA states that they are in fact unsure of the optimal dosage and period of treatment with hydroxychloroquine sulfate, suggesting that health care personnel can prescribe the medication to combat the effects of the virus. The FDA however, does discuss the drug interactions to ensure patients with preexisting conditions medications do not have adverse effects after taking the prescription. This example, although seemingly irrelevant, has much connection to diseases such as lupus and RA.

Hydroxychloroquine a big question mark fro Covid-19

The coronavirus pandemic as a whole has caused panic to the severity that people, those of which with means, have stockpiled hydroxychloroquine and toilet paper among other

things. People are doing so, again as the FDA was careful to assert, under the assumption that it may treat COVID-19 case.

The assumptions are premature as clinical testing is still being conducted and will continue. Unfortunately, the result of this mass hoarding has caused unforeseeable shortages in hydroxychloroquine for people with preexisting conditions aside from COVID-19. Now tying in the objectives of the paper, these persisting conditions include malaria, Lupus, and RA. As hydroxychloroquine is streamlined for various ailments, shortages provide dire consequences for people that need it most and have proven its efficacy, not simply its efficacy based on assumption. Ultimately, the current global events have taught the world that more funding must go towards health care and drug discovery. Alternative routes of medicine and treatment could possibly thwart the next global panic that comes with a heath event.

With more research and review output, it holds the power to bring the scientific communities to some degree of resolve. There is no telling whose eyes will come across your paper and essentially prompt scientific investigation. Specific to this paper, two alternatives to hydroxychloroquine will be discussed and compared to each other. Drug delivery using synthesized hyaluronic acid will be compared in two forms. Injections compared to hyaluronic acid-coated lipid nanoparticles.

Injections to treat Rheumatoid Arthritis

More recently, after FDA approval, a new class of drugs that encompass the form of injections used as inhibitors for targeted pain relief. These injections were revolutionary as they were a way to broadcast the medication to one area and ensure the most optimal bioavailability. The injections could be administered at a hospital or more frequently at doctors' offices proving the prevalence and commonplaceness of the drug intervention. The caveat to the injections, however, is the short-lived relief time. Moreover, as a form of continual treatment, the effects decrease with times as the body becomes increasing used to the drug.

Traditional drug delivery systems for RA

Discussion of traditional drug delivery methods paves way to understanding the new technologies and increasing appreciation for the depth of scientific discovery. Compounding involves taking a powder and forming it into a liquid, this is the convention for making antibiotics or antivirals. Compounding pharmacies still exist as most community pharmacies no longer do it in house. This is due to the fact that small scale manufacturing must follow specific regulations while being time consuming, hence prices are high for these products. This rather elementary example demonstrates how the effect of pricing can place limitations on the economical side of pharama. Similarly, nanotechnology as a new science is exceptionally expensive. From sourcing the biomaterial, to the scientists, and finally facilitating the laboratory operations, the entire enterprise is costly to not only wallets but time. Nevertheless, these aspects are what fathom its intrigue.

Understanding RA

Before formally making a distinction between the two drug delivery techniques, there is a need to discuss rheumatoid arthritis as a single unit of a disease. Upon investigation of the research topic I took to google to find some general facts about RA. To my expectation, popular searches included asked difference between arthritis and rheumatoid arthritis. Another frequently asked question asked the overlap between lupus and RA. These questions presented a great starting point as it boarded the implications of this review. The more discovery and intervention given to RA could in fact equate to treatment for Lupus. The two autoimmune conditions present such overlap that they are readily confused for each other when investigation joint pain and inflammation. Ultimately, although the two diseases are distinct, prompting the research one on condition brings valuable insight to the other. With this underlying understanding, RA is the basis of the review with Lupus treatment as an underlay.

RA as a progressive disease, meaning that it does not relive itself. It affects the joints though inflammation and deterioration of joint lining. Without the cushion of lubricated joins, pain is heightened, and discomfort is a 10. Drug intervention techniques includes prescribing anti-inflammatories and steroids. Other means including medication to suppress the immune system to limit the natural bodily response of inflammation. Hyaluronic acid had showed promising results compared to taking prescribed oral tablets that have short lived effects. The acid intervention has seen statistically significant clinically trials to been to treat RA as opposed to antirheumatic drugs taken orally. The two types of hyaluronic acid drug delivery will be addressed within this paper and the. Injections compared to hyaluronic acid-coated lipid nanoparticles.

Research Methodology

In order to find applicable and accomplished sources, I took use of two databases in particular that I had access to. These of which included "Taylor & Frances online" as well as "US National Library of Medicine National Institute of Heath" database. Sources from these databases provided both published and peer reviewed articles as well as scientific clinical trials. The introduction of paper takes a broad to narrow approach by discussing the discussing the scientific relevance of drug discovery in today's everchanging world and systematically applies it to rheumatoid arthritis. A top down processing approach was used to write this review article in an effort to narrow down topics from broader and more inclusive topics. It is significant to note that the paper will address rheumatoid arthritis with the acronym "RA". More encompassing, discussion of COVID-19 initiates the conversation about RA and the underrepresented need for drug discovery and pharmacokinetics.

Connections with Lupus are also acknowledged through the paper by drawing overlap between the two autoimmune conditions.

Conventional methods of RA treatment will be discussed and placed against the new technology invested in nanoscience. The first article to be reviewed was a 2008 study titled "Effect of Intra-articular Injection of Hyaluronic Acid in Rheumatoid Arthritis Patients with Knee Osteoarthritis". The second article communicated is "Studies of Hyaluronic Acid in Rheumatoid arthritis" published in 1956. Switching gears, to discuss modern day injections for RA used and marketed, the medical review done for an immunosuppressive drug called Kevzara® was investigated. Finally addressing the nanotechnological innovations, a 2017 article titled "Targeted delivery of hyaluronic acid-coated solid lipid nanoparticles for rheumatoid arthritis therapy", guided discussion of how contemporary clinical trial are being funded to create future standards of care for RA and other autoimmune conditions.

Injections

A study was done in coordination with the official veteran's hospital in Taipei, Taiwan and the National Yang-Ming University School of Medicine. They were successful in creating a study done to assess the "Effect of Intra-articular Injection of Hyaluronic Acid in Rheumatoid Arthritis Patients with Knee Osteoarthritis". Their 2008 study was completed by taking 20 patients diagnosed with RA and dividing them into two groups that of stage two and stage three. As pain cannot entirely be quantified as it remains entirely subjective, the researchers distinguished the two groups based on the Kellgren and Lawrence system to classify osteoarthritis4. The classification method groups patients suffering from knee osteoarthritis by separating them on a scale of one to five equating to the five groups on the scale. It is significant to acknowledge that osteoarthritis affects a single joint such as the knee but RA affects most joints in the body. Nonetheless, the findings of the study demonstrated the initial promising nature of hyaluronic acid injections.

After placing 11 of the 20 patients in group two, the remaining patients were classified as group three with more severe knee osteoarthritis. All patients were given the same dosage of the intra-articular, or within the join, injection of hyaluronic acid that had been purified and made feasible for human absorption. With no statistical difference in groups two and three, the acid treatment was found to be beneficial to the patients that suffered with RA. More specifically, starting from week five of the trial, notable differences in pain decrease were recorded using the WOMAC index. The WOMAC index, as a questionnaire quantified a patient's pain with osteoarthritis as a productive way to quantify pain. The p-value for statistical significance at week five was found to be ($p<0.0167$) and actually persisted until week nine at the same p-value3. As the injection was given at the knee joint once a week for the duration of the experiment, the exogenous hyaluronic acid synthesized was used to promote the production of endogenous hyaluronic acid as if almost a catalyst. Thus, the result was reduced synovitis as the immune response of inflammation was activated much less. Overall, the results from this study can be conclusive to suggest the favorable outcomes of injections. Shortcomings of the study, however, was the relatively small survey size and lack of control group. The later, a control group, could have been beneficial by addressing a placebo set. This would accommodate for bias in the study if the placebo group noted positive results.

Hyaluronic Acid History

Dated back to 1956, a study conducted by a Swedish medical department investigated the hyaluronic acid naturally occurring in human bodies. The study concluded, "It appeared to us that determination of the degree of polymerization of the hyaluronic acid might provide a convenient objective record of the effects of therapy in joint diseases" [1]. The study took samples of synovial joint fluid from 500 individuals suffering from RA and other various joint diseases. The samples were then treated with hydrocortisone injections that were given intra-acicularly in order to observe the difference the hyaluronic acid in the synovial fluid. This was done to test the best method for reducing the effects of RA and come to a consensus for streamlining treatment. The study revealed that a change in hyaluronic acid are noted when the viscosity of the synovial fluid change. Moreover, hydrocortisone injected to the knees was found to restore the hyaluronic acid within the synovial fluid samples.

This study essentially paved the way for corticosteroids to be the standard of care for the reduction of inflammation. Modern day medications include Prednisone, which was approved by the FDA in 1955, for example which is also taken by Lupus patients. During 1956, when the study was officially published, the technology to synthesize hyaluronic acid simply had not been created. In was not until 1964 that hyaluronic acid was synthesized in vitro in a laboratory. The event essentially set the tone for future RA treatment and cosmetic procedures.

Modern Day Medicine

In more recent times, as of 2017, the FDA finally approved a drug called Kevzara®. The sarilumab injection could be self-administered in the targeted joint area in order to reduce immune system inflammation response. The IL-6, also known as interleukin 6 is a protein secreted by the immune system in order to promote cell to cell communication5. To suppress the immune response that is the body's natural way of maintaining homeostasis, anti-IL-6 receptors act as antibodies. With the anti-bodies binding to the IL-6 receptor cites, IL-6 proteins cannot communicate the signal to activate the body's inflammation. Clinical reviews revealed that as the anti-bodies bind to the receptor, this inhibits IL-6

mediated signaling. More explicitly, Kevzara®'s pharmaceutical team submitted to the FDA, "Sarilumab is a recombinant human immunoglobulin (IgG)1 monoclonal antibody that binds specifically to both soluble and membrane-bound interleukin-6 (IL-6) receptors (sIL-6Rα and mIL-6Rα) and inhibits IL-6-mediated signaling" (Peng 2). Thus, productively suppressing RA discomfort as well as other inflammatory diseases.

Not surprisingly, Kevzara® (sarilumab) injection has become the center of many preliminary COVID-19 clinical tests. Researchers are trying to use the IL-6 anti-bodies to aid hospitalized COVID-19 patients in ongoing clinical tests to thwart the immune response occurring with pneumonia (Pharmaceuticals 2020). Addressing the shortcomings of this type of injection, a holistic review is needed. Patients must understand that immunosuppressant drugs, in any form can deter the body's ability to fight infection. These of which include tuberculosis and certain fungal infections.

Hyaluronic Acid Coated Lipid Nanoparticles

Hyaluronic acid, although naturally derived in the body, can be sourced in a laboratory setting. When production by the body occurs in lesser quantities, pharmaceutical grade hyaluronic acid becomes of more precedence. Using modern day standards of care for RA patients, nanotechnology heightens the effect of treatment and longevity of pain relief. Continuing on with more advanced method of drug delivery, nanotechnology has been able to take commonly taken glucocorticoid prednisolone and heightening its results. As stated by article published in April of 2020, "Glucocorticoids (GCs) are a group of drugs structurally and pharmacologically similar to the endogenous hormone cortisol with various functions like anti-inflammatory, immunosuppressive, anti-proliferative, and vaso-constrictive effects" [2]. The adverse effects of traditionally taken corticosteroids pose certain health risks including changes in weight, mood, different types of edema, and disturbances in sleep just to name a few.

Moreover, to address the prolonged biological effects of glucocorticoid prednisolone by itself, sans nanoparticles, skeletal effects include lone in bone density if the corticosteroids are taken in high doses for a prolonged amount of time. This, in effect can cause further pain in joints and make day to day activities increasingly difficult. Taking into consideration a biopsychosocial lens, the effects on quality of life are immense if these side effects of prolonged corticosteroid usage occur. Myopathy, that of muscle deterioration and infectivity, can also arise as a consequence. This type of deterioration is called steroid-induced myopathy. Also, as a general overview, infections are common among the group of people under question.

To thwart these of some, if not most of these effects, nanotechnology is able to encapsulate the steroids to increase surface area and increase potency. In further detail, solid lipid nanoparticles made up of the prednisolone steroid, when covered in hyaluronic acid, can treat RA. An article published on targeted drug delivery found that, "As predicted, HA-SLNs/PD particles accumulated in affected joint tissue after intravenous injection into mice with collagen-induced arthritis (CIA), and HA-SLNs/PD persisted longer in circulation and preserved bone and cartilage better than free drug or drug encapsulated in SLNs without HA" [3].

Explained more in depth, receptor for the hyaluronic acid is identified as CD44. With recent discovery done by cell developmental biologist, CD44 has been found to be overexpressed in cancer cells. This particular antigen promotes cell to cell interaction in ways to improve cell proliferation. A piece on the CD-44 receptor expressed, "Its interaction with appropriate extracellular matrix ligands promotes the migration and invasion processes involved in metastases" [4]. The commonality of over expression is also seen in synovial membranes, macrophages and fibroblasts. These too have an increased presence of the CD-44 receptor sites. The article published on targeted drug delivery stated, "Activated macrophages are the main effectors of inflammation in RA: they continuously release several pro- inflammatory cytokines, which aggravated the progress of RA" [5].

In order to test the effect of the solid lipid nanoparticles, the study conducted in 2017 tested the new form of targeted drug delivery on a population of mice. The mice were treated with a specialized collagen in order to induce arthritis and hence makes notes on the observations. To provide a conclusive result, the study showed that the mice had a preserved both bone and cartilage better. This was only true because they were treated with hyaluronic acid solid lipid nanoparticles with glucocorticoid prednisolone. The particular experiment was also able to conclude that the prednisolone given to the mice in solid lipid nanoparticles was not as effective when the hyaluronic acid did not coat the particles. Thus, demonstrating the fundamental need for hyaluronic acid as an active ingredient for the treatment.

Referring to the methods of the experiment as a whole, intravenous injections were used as a significant part of the research design. Use of intravenous injection is a step up from the conventional drug delivery technique of intra-articular injection for targeted drug delivery. Injecting a particular area repeatedly leaves room for future complications such as infection and busing. Moreover, as behavior is an unforeseeable circumstance, people may be more reluctant to receive the intra-articular injections frequently when they are already experiencing such joint pain. As can be explicitly understood, simply changing the injection methods offers a broad range of benefits.

Digging deeper into the experiment's materials preparation, the lipid nanoparticles were coated hyaluronic with a 99.9% purity. This process was completed through electrostatic interactions.

These interactions occur are the basis of chemistry in which the positively charged nucleus of the molecule in question id treated with negatively charged nucleophilic electrons. The result is a reaction in which bonds are created and a new molecule is formed with different properties that its ions and elements. The process is demonstrating an aspect of green chemistry as no solvent was used. Moving forward, the solid lipid nanoparticles that encompassed the glucocorticoid were synthesized with use of film ultrasonication. Here it is the use of sound, its vibrations, and solvents that creates new fused particles. Ultimately, the process of creating the drug in its entirety, although not economically friendly, increased the bioavailability of the acid coated lipid nanoparticles. Thus, by only targeting inflamed tissue, the potency of the drug is able to be retained. The study concluded that "We measured their levels in arthritic mice treated with HA-SLNs/ PD as another index of therapeutic efficacy. Levels of all three cytokines in serum were significantly lower in animals treated with HA-SLNs/PD than in animals treated with free drug or SLNs/PD ($p<.05$)" [6]. It was through measurement of the inflammatory cytokines that the efficacy of the procedure was noted, and the desired outcome was verified.

Conclusion

Conventional approaches for RA treatment are the standard of care. According to the American College of Rheumatology, "The 2015 ACR RA treatment guideline addresses the use of DMARDs, biologics, tofacitinib, and glucocorticoids in early and established RA and the use of various treatment approaches in frequently encountered clinical scenarios, including treat-to-target, switching between therapies, tapering of therapy, the use of biologics and DMARDs in high-risk RA patients" [7]. These courses of treatment have provided some relief to RA patients but little longevity of relief. To accommodate for this, injections of both hyaluronic acid make up and anti-IL-6 antibodies became more common as a form of targeted drug delivery.

The traditional methods, as they have been the standard of care for such a long duration of time, are dated as they pose various other health related ailments and side effects. Time presented patients who were able to show long term effects of the steroid treatments and adverse side effects discussed earlier in the paper. Orally ingested medication for RA treatment have low bioavailability due to absorption by the stomach lining, and hence there is decreased potency of the active ingredients that actually target the receptor sites. A new class of drugs in the form of injections not only thwart the issue decreased bioavailability, but also lessen the adverse side effects of non-targeted therapy. Acting faster and more effectively, both hyaluronic acid injections and anti-IL-6 antibody injections are currently used and will continue to be used in conjuncture with the oral RA medication until nanotechnology can become the standard of care.

As a formal overview of drug delivery systems in term of the nano interventions, they pose multifarious beneficial attributes. These of which include reducing the side effect and toxic responses of traditional oral delivery measures such as tablets, gel pills, and liquids for reference. The side effects of one pill to bring relief to a specific ailment may in fact require another pill to combat the side effect of that medicine. More times than not mediation medication is prescribed to lessen the mal secondary responses. This phenomenon often leads to over prescribing pharmaceuticals and liver damage in extreme case. Significant to older populations of people, specifically those over 65, are found to be taking 15-18 prescriptions per year based on surveying and thorough medical panels. The high volumes of medications inevitably lead to complications with the kidneys and liver. Moreover, the more medication that is prescribed to individual the greater and more dire the need for communication between health care providers. The formal communication is necessary to ensure drug safe pharmacokinetics and drug to drug interactions. A synergistic effect can occur when the body acts as if a melting pot for pharmakon.

Continuing discussion about the assets of nano drug delivery systems, drugs encapsulated with nanoparticle antibodies can target specific receptors and active sites. This revolutionary mechanism is tested through various types of spectroscopies including protons and carbon NMR as well as IR and EPR signals. The nanoparticles can be incorporate in various form including but not limited to liposomes, solid lipid nanoparticles, nanohydrogels, nanofibers, nano scaffolds, polymeric nanoparticles, and inorganic nanoparticles. With various particles of increased surface areas, these nanomaterials are made up of different biomaterials and polymers.

With little argument, it can be concluded that nanotechnology is the better and more successful alternatives based on clinal testing done and promising results seen through the 2017 study titled "Targeted delivery of hyaluronic acid-coated solid lipid nanoparticles for rheumatoid arthritis therapy". Moreover, biomaterial engineering verified, "In comparison with traditional formulations, nano- and micro-technology, hydrogels and liposomes have already demonstrated their superiority in retarding kidney filtration, extending drug residence time and in turn getting better therapeutic efficiency, enhancing patients' compliance" [8-12]. Placed in contrast with existing therapeutic drugs, nanotechnology allows for green synthesis as long as biodegradable materials are used, and toxic waste products are not synthesized.

The limitations of nanotechnology lie in the essence of time. As a new science, there has not little intervention done in order to track the lasting effects of nanomaterial. As more FDA approvals are set, long term affects can be acknowledged in humans, the environment, and the economy. For now, nanotechnology remains reserved for those who can afford to venture its advantages. In relation to the

acid-coated lipid nanoparticles seems promising in RA treatment as indicated by populations in mice with induced arthritis. Speaking of the data found in the mice study, "Targeted delivery of hyaluronic acid-coated solid lipid nanoparticles for rheumatoid arthritis therapy", pro-inflammatory cytokines appearance was recoded. Four sets of mice were treated with different injections. Group A were given an injection of saline while group B were given glucocorticoid prednisolone. Group C was given solid lipid nanoparticles with glucocorticoid prednisolone, and group D was given the hyaluronic acid-coated solid lipid nanoparticles with glucocorticoid prednisolone. These groups were all plotted against a control group of mice with induced arthritis given no form or drug. Outstandingly, group D was found to have a score of two in terms of histopathology. This meant limited pannus formation. After amazing the data of the clinical trial, the statistical significance of group D was found to be ($p<-0.05$). Although the data supports the theory that solid lipid nanoparticles are seemingly safe and effective, artificially produced join pain in mice however varies distinctive with arthritis in humans. The call to action this paper brings to light the need for further pharmacokinetic drug testing and advocacy. As RA has overlap with other autoimmune diseases, RA drug discovery could in fact results in forward treatment of Lupus and osteoarthritis.

References

1. Chen-Liang Chou , Han-Wen Li, Si-Huei Lee, Ko-Lun Tsai, Hsiao-Yi Lin (2008) Effect of Intra-articular Injection of Hyaluronic Acid in Rheumatoid Arthritis Patients with Knee Osteoarthritis. J Chin Med Assoc 71(8): 411-415.
2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1006909/pdf/annrheumd00179-0064.pdf.
3. https://www.fda.gov/media/136537/download.
4. Mark D Kohn, Adam A Sassoon, Navin D Fernando (2016) Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. Clinical Orthopaedics and Related Research 474(8): 1886-1893.
5. Kou Longfa (2019) "Biomaterial-Engineered Intra-Articular Drug Delivery Systems for Osteoarthritis Therapy." Drug Delivery, vol. 26, no. 1, Jan. Taylor and Francis Online, pp. 870–885.
6. https://www.britannica.com/science/interleukin.
7. https://clinicaltrials.gov/ct2/show/NCT04315298.
8. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761037Orig1s000MedR.pdf.
9. A Multifunctional Cell Surface Adhesion Receptor Is a Regulator of Progression and Metastasis of Cancer Cells. Frontiers in Cell and Developmental Biology.
10. Jasvinder A Singh, Kenneth G Saag, S Louis Bridges, Elie A Akl, Raveendhara R Bannuru. Et al. (2015) "2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis." American College of Rheumatology: Arthritis Care & Research 68(1): 1-26.
11. Muhammad Yasir, Amandeep Goyal, Pankaj Bansal, Sidharth Sonthalia (2020) Corticosteroid Adverse Effects.
12. Meiling Zhou, Jierong Hou, Zhirong Zhong , Na Hao, Yan Lin, et al. (2018) Targeted delivery of hyaluronic acid-coated solid lipid nanoparticles for rheumatoid arthritis therapy. Drug Delivery 25(1): 716-722.