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Analysis of Treatment of Polymyalgia Rheumatica

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ABSTRACT

The study presented below investigates the different treatment options as well as the medications used when dealing with polymyalgia rheumatica. Polymyalgia rheumatica (PMR) is an autoimmune inflammatory condition that is often characterized by stiffness in the joints, specifically the hips or shoulders. This disease is most often observed in those that are older, as it is seen that the likeliness of this disease increases with age. Multiple medications are available on the market to treat PMR, but prednisone is the option that is typically first used by doctors. There are base guidelines that may be followed when prescribing these medications to patients, although they vary on a patient-to-patient basis. Part of this regimen will be tapering eventually, slowly lowering the dose over the weeks taking the medication.

Keywords: Polymyalgia Rheumatic; Different Medications for Polymyalgia Rheumatic; Aging Populations; Stiffness in the Joints; As Extreme Fatigueless; Weight Loss

Abbreviations: PMR: Polymyalgia Rheumatica; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; GCA: Giant Cell Arteritis; EULAR: European League Against Rheumatism; ACR: American College of Rheumatology; JAK: Janus Kinase; FDA: Food and Drug Administration

Introduction

Polymyalgia rheumatic (PMR) is an inflammatory disease that is characterized by stiffness, appearing often in the hips and the shoulders. This stiffness experienced is most often worst in the morning and the severity decreases as the day goes on. There are ill-defined symptoms that may accompany this stiffness, such as extreme fatigue or weight loss. Patients suffering from PMR can experience difficulty performing day to day activities, such as getting dressed or even reaching for items on a shelf. Studies performed in the lab can be helpful in terms of diagnosis or state of the disease of PMR, or to rule out PMR [1]. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are laboratory tests that can be used to help identify and diagnose this disease. PMR primarily occurs in those greater than 50 years of age, and as age increases the likelihood of experiencing this disease increases. After much research and studies, there are multiple suggested causes of PMR. Some of these causes are suspected to be genetic while others environmental. One such theory involved a specific gene, HLA-DR4, where this genotype may be responsible for such disease [2]. There has also been discussion of a possible external factor that need further investigation due to the disease incidence being higher in Nordic countries compared to Asian, Mediterranean, and MidEastern countries [3]. There is a close relationship between giant cell arteritis (GCA) and PMR, as there is much overlap in the diagnosis of each disease [4].

There are multiple options when it comes to the course of action to treat this disease. The typical treatment of PMR initially starts with the use of oral glucocorticoids [5]. Second line agents may be used for those that are unable to tolerate oral glucocorticoids or relapse, which there are several of. These medications are often required for several years and can result in side effects. The average treatment lasts around one to two years, but when the steroids are tapered before symptoms improve can result in a relapse [1]. Using other medications such as methotrexate, and others, can be employed if several relapses have occurred in a patient with PMR [1].

Treatments used Polymyalgia Rheumatic Diseases

Prednisone is the first line therapy for PMR, so when discussing options of treatment this will be heard often. The European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) have created recommendations for the treatment of PMR, which should be modified for patient specificity [6]. According to the guidelines that are followed in terms of prescription, the typical initial dose for prednisone to treat PMR is around 12.5 to 25 mg a day [1]. PMR patients will generally rapidly respond to doses of 12.5 to 25 mg of prednisone daily [5]. There are theories that other factors may affect treatment outcomes in patients with PMR, such as weight of the patient and age. In a study including 42 patients, where 28 were of an age greater than 60 and 14 were of an age younger than 60, some differences were seen when taking the same dosage of prednisone. [7]. Through analysis with CT imaging inflammation was analyzed between the two groups, and the score was lower for the group under 60 compared to those over 60 [7]. A study performed over a course of 15 years showed that the incidence rate of PMR increased with age after 60 but appeared to drop off at around 80 years old [8]. This shows that although incidence rate of PMR occurs as patients grow older, it may not be completely linear as some studies show it eventually slows down or drops off. In the younger group of a study performed it was found that the introduction of DMARD's occurred three times more often than the older group [7]. This may show that a dependence on corticosteroids may be more likely in younger patients.

The so-called younger patient population also was found to have more resistance to prednisone during treatment of PMR [7]. A correlation has been seen between bodyweight of the patient and treatment of PMR with prednisone as well. A study of 60 PMR patients that tested a starting dose of 12.5 mg daily, had a response rate of 78.3% [9]. The only correlation from the study that could explain this response found, is that patients with lower body weight resulted in a higher response, therefore an optimal weight-based dose of 0.2 mg/kg was concluded [9]. Induction dosing may be based on a variety of aspects such as BMI or symptom severity, patients with a smaller body habitus or less severe symptoms may be considered for a smaller dose of prednisone [1]. This was in comparison to those with a much larger body, when 20 to 25 mg of prednisone a day is considered [1]. Drawing conclusions from an experiment performed based on weight, it is seen that the main factor that contributes to steroid response in treatment of PMR is the bodyweight of the patient [1]. Once a patient has responded to the initial steroid dose, a tapering schedule can be used and begin. Tapering is evaluated based on the symptoms presented, thus it is patient specific and must be planned individually. Once symptoms are under control and the pain and stiffness from PMR has been resolved for multiple weeks, prednisone may be decreased every 2-4 weeks at an increment of 20% [1].

When a dose of 10 mg is achieved by a patient, tapering changes to a decreasing increment of 1 mg every 1-2 months until off all together [1]. A regimen has been proposed by the British Society of Rheumatology, which says that prednisolone should be taken over the course of 3 weeks at doses of 15 mg daily [10]. In terms of tapering, the dose should be lowered to 12.5 mg daily for another 3 weeks, which is followed up by a dose of 10 mg daily for an additional 4-6 weeks, and finally a reduction of 1 mg daily for the final 4-8 weeks [10]. Tapering schedules vary depending on the source, but in the end show similarities in terms of the doses given to patients. Another tapering schedule starts with 12.5 to 25 mg daily of prednisone, and then tapered to 10 mg daily for 4-8, and once again decreased by 1 to 1.25 mg daily every 4 weeks [11]. Around half of the patients on this form of treatment may experience a complete resolution of symptoms, alternative measures may be taken such as intramuscular forms of medicine as well in higher doses [11]. Many times, patients must stay on glucocorticoids for extended periods of time due to relapse once tapering of medications begins. Relapse can be defined as the reappearance of symptoms and elevated inflammatory markers, which requires raising the dose of prednisone back to the previous efficacious dose before tapering occurred [10]. A study of 57 PMR patients described a greater risk of relapse if findings of a positive power Doppler show inflammation in the shoulders [1].

A study performed showed that there is a correlation between relapsing during treatment and the initial dose as well as the speed of taper, as a higher initial dose and quicker tapering appeared to raise the chances of relapse [1]. Majority of relapses appeared in patients while taking doses less than 5 mg of glucocorticoids, and ESR appeared to be much higher than CRP during the first 3 months of treatment [12]. A study screening 6031 articles found that CRP, ESR, and patients' pain are important factors when defining patients' remission or relapse [13]. A study of 284 patients also showed that a greater initial starting dose of prednisone as well as faster tapering of the dose, showed a higher relapse rate [14]. The data collected showed a 7% increase in relapse risk for every 5 mg daily increase of initial dose [14]. When the tapering rate was considered to be fast, it was four times more likely that a relapse would occur, while when the rate was considered to be medium, it was found to be twice as likely [14]. Glucocorticoids are not without side effects, thus it is always recommended to take the lowest dose possible that still gives results, when establishing a patients medication regimen.

Use of Methotrexate, Azathioprine, or A TNF Inhibitor

Medications such as, methotrexate, azathioprine, or a TNF inhibitor, may be used for a patient that has experienced 2 relapses, as these are steroid sparing [1]. A study was performed in a retrospective fash-

ion on patients with steroid resistant PMR, by looking into the steroid sparing effect that methotrexate had on them [15]. In simple terms a steroid sparing agent is one that may be used in the scenario that the common steroids used to treat the symptoms is ineffective, thus it is steroid sparing. Methotrexate, being a different form of treatment, may not follow the same regimen as those on prednisone, so a new plan may need to be created. In clinical trials performed analyzing the effects of certain steroid sparing agents, methotrexate can be seen at doses around 7.5-10 mg a week [6]. This 7.5-10 mg weekly is much lower than what we have seen as a starting dose for prednisone, which was usually anywhere between 12.5 and 25 mg weekly. In one of the studies performed the timeline for the steroid sparing effects of methotrexate was analyzed, which found that it was effective at both 6 and 12 months of treatment. There are also scenarios where a patient may take both prednisone, which is a glucocorticoid, and methotrexate, a steroid sparing agent, at the same time. A double blind, randomized, and placebo controlled trial was performed to see the effects of adding methotrexate to a prescription of prednisone had on the symptoms of PMR patients.

In the end it appeared that the methotrexate on top of the prednisone had an effect on the patients' health, as 28 of 32 using the methotrexate were off prednisone at 76 of treatment, while only 16 of 30 in the placebo taking group [16]. In these kinds of experiments side effects of these treatments must be analyzed as well to compare the risk and reward ratio of the treatment. In this particular experiment more adverse effects were recorded in the group taking the methotrexate compared to the placebo, with 42 being recorded from the methotrexate group compared to the 34 from the placebo group.

Use of JAK Inhibitors

JAK inhibitors have been studied in PMR. Patients with a recent diagnosis of PMR, were found to have different gene expression than the control group of patients that had increased expression JAK2 and other genes [17]. A Janus Kinase (JAK) is a non-receptor tyrosine kinase that is multidomain and have an import role in the transduction of signals throughout cell [18]. JAK inhibitors used in a wide variety of medications and have a variety of uses in the medical world. For PMR though the JAK inhibitor that will be seen the most used in treatment would be tofacitinib. Tofacitinib acts as a JAK inhibitor by suppressing a specific pathway downstream, which in turn diminishes the PMR activity occurring [19]. There may be evidence that the use of some JAK inhibitors can be just as effective as glucocorticoids at treating some autoimmune diseases. In a study comparing the effects of tofacitinib and glucocorticoids on newly diagnosed PMR patients, 35 receiving tofacitinib and 32 receiving glucocorticoids, the effects on PMR-AS were very comparable at 12 and 24 weeks [17]. There have also been studies into the side effects of such medications, as their use may not be applicable if they are deemed too dangerous to give to patients. In a randomized and open label control trial, it was found that the risk of malignancies in those with RA was higher when taking tofacitinib compared to tumor necrosis factor inhibitors, excluding NMSC [20]. Tofacitinib may be seen being taken at a lower dose than glucocorticoids, in a study using both tofacitinib was taken 10 mg daily while prednisone was taken 15 mg daily [19]. When looking into the safety of both GC's compared to JAK's, a study found that the group taking glucocorticoids showed 11 new cases of hyperlipidemia, while the group taking tofacitinib only had 4 new cases [17].

Recent Applications of Biologicals for PMR

The biological disease modifying medication tocilizumab has been studied in the treatment of polymyalgia rheumatica. Tocilizumab competitively inhibits the interleukin (IL-6) receptor. One setback of such medications is the price, as cost is often a consideration when using these kinds of biological agents. Patients with new onset polymyalgia rheumatica were treated with monotherapy of tocilizumab for three doses followed by prednisone for 12 weeks with all the patients reaching the primary endpoint goal [21]. Patients on glucocorticoids were give tocilizumab or placebo for 24 weeks in addition to glucocorticoids [22]. The primary endpoint goal was reached in 63.7% of the treatment group, compared to only 31.4% of the placebo group reaching this goal [22]. Tocilizumab when combined with glucocorticoid has shown promise as being an effective treatment agent for polymyalgia rheumatica [23]. An aggressive dosing regimen of tocilizumab as monotherapy may be an option for those who are unable to take glucocorticoids [24]. The frequency of infusions is yet to be determined for treating polymyalgia rheumatica [24]. Tocilizumab therapy is not without the occasional side effects in patients using it in their regimen. Adverse events of leukopenia have been observed in tocilizumab therapy prompting a dose reduction from 8 mg/kg to just half of that at 4 mg/kg every 4 weeks [21]. Adverse effects of both neutropenia and leukopenia has been recorded in polymyalgia rheumatica patients receiving tocilizumab [21].

Tocilizumab can cause adverse effects of upper respiratory infections and nausea [25]. Recently the U.S. Food and Drug Administration (FDA) has approved a biological agent, sarilumab, for the use of treating PMR when patients are unable to take glucocorticoids. Interleukin-6 (IL-6), a cytokine, has been observed to be raised in patient with polymyalgia rheumatica [26]. In a randomized study patients were assigned to either placebo and a 52-week glucocorticoid taper or sarilumab for 52 weeks and a glucocorticoid taper for 14 weeks [27]. Sustained remission was the primary outcome, and it was achieved in 28% of the treatment group compared to 10% of the placebo group [27]. When used for the treatment of rheumatoid arthritis, sarilumab had similar adverse effects compared to tocilizumab, but sarilumab had an increased risk for neutropenia [28,29].

Conclusion

The study performed has come to multiple conclusions about the medications used as well as the treatments for polymyalgia rheumatica. One general trend seems to be the initial use of prednisone as the

first step to treating this disorder. Tapering can also have an effect on the symptoms that a patient experience. The speed that the medication dose is tapered can cause a potential relapse if it is tapered too fast. Some medications that have been suggested to help with the disorder, have shown negative side effects that have deemed them unsafe to use as a form of treatment. Overall, many different paths may be taken when prescribing medications for patients experiencing PMR.

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