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Review Article

Twenty First Century Treatments for a Nineteenth Century Disease: Polymyalgia Rheumatica

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Abstract

Objective: Polymyalgia Rheumatica (PMR) was first described in the 19th century in five elderly men in the Scottish spa at Strathpeffer by Dr. William Bruce [1]. The treatment of this common, painful, disabling condition has been corticosteroids virtually since these were first introduced to clinical practice 70 years ago [2]. This condition is the commonest reason for long term use of corticosteroids in the elderly. The side-effects of these agents are severe, and this is especially true in older age groups. The recent introduction of biological Disease Modifying Antirheumatic Drugs (DMARDs) and newer synthetic DMARDs has raised hope that effective treatment of PMR can be offered, and the serious side-effects of traditional steroid treatment circumvented. This review offers a summary of recent attempts to use these new antirheumatic agents.

Methods: The authors searched Medline and PubMed using the search items polymyalgia rheumatica, giant cell arteritis and temporal arteritis over the past fifteen years. As much as possible, this search focused on treatment of PMR and Giant Cell Arteritis (GCA) with corticosteroids and newer synthetic and biological DMARDs where outcomes including toxicity and side-effects could be assessed.

Results: The reports in the literature of the exhibition in PMR of a wide range of treatments including the newer organic and biological DMARDs have been reviewed. To date no entirely satisfactory alternative to corticosteroids for the control of this disease has been reported.

Conclusion: Some of the newer DMARDs have shown promise in the management of PMR but, to date, no agent has been found adequate to replace the use of corticosteroids in the treatment of this disease.

INTRODUCTION

PMR was first described in 1888 by William Bruce [1], a Scottish physician, in five men of advanced years who had the very characteristic symptoms of severe pain in the muscles of the proximal limb girdles, especially that of the upper limbs. Bruce noted that, in spite of the severity of their symptoms, there were no objective signs of joint disease and recovery was universal within two years. Bruce's series proved atypical in that PMR is now known to be much more prevalent in women and remission by two years occurs in most patients but is not universal, but otherwise his description of the disease remains remarkably accurate today. There is a close association between PMR and GCA. This disease was also first described in the last years of the nineteenth century by Hutchison [2] but the classic features of GCA were more fully delineated by Horton and his colleagues [3] forty years later. Throughout its history PMR has been linked to GCA [4,5], and many believe these two entities represent different aspects of the same pathological process. This is because many patients have features of both diseases, and both diseases show consistent and rapid response to treatment with corticosteroid drugs [6], although the doses used in GCA are much higher than those used in PMR [7,8]. As a result, many papers do not distinguish between these disorders, and this can lead to difficulty in assessing the efficacy of treatment of both. It seems most likely that PMR and GCA are different, but closely associated, diseases of the elderly [9]. There is some evidence that the populations affected by these two diseases differ genetically as assessed by the markers of disease susceptibility [10-12]. As no direct cause of either disease is known it remains possible that they represent different responses to a single aetiology.

Polymyalgia Rheumatica: A Complication of Virus Disease and/or Vaccination?

The aetiology of polymyalgia rheumatica is unknown. Both genetic and infective aetiologies have been postulated but the evidence supporting these hypotheses is not very convincing. It has been well reviewed by Salvarani and his colleagues [12]. However, the recent Covid-19 pandemic has offered some additional evidence that this disease may follow virus infections and/or vaccinations [13-17] to date there is no information of the effects of anti-viral medications on the incidence or severity of PMR.

Treatment of PMR

Physical treatments and spa therapy: Bruce [1] did not have the option of modern pharmacology to treat his patients, but he did use the physical treatments available at the Strathpeffer spa. He did not report on any short-term benefit this afforded his patients, but he did note that all of them had complete remission of their symptoms after two years. Although by no means universal, a similar remission is expected in the great majority of PMR patients today [8]. It is difficult to determine whether the cold waters of Bruce's Scottish mountain spring were even partially responsible for the remission in his patients. Spa treatment has been shown to be beneficial in other rheumatic diseases such as rheumatoid arthritis, osteoarthritis and spondyloarthritis [18-20]. However, few patients with PMR in most modern reported series undergo similar spa therapy. It has been reported that treatment with acupuncture and homeopathy may also add benefit in the treatment of inflammatory arthritis, but no reports of such an effect in PMR have been found [21].

Traditional Pharmacological Treatments of PMR and GCA

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Prior to the introduction of corticosteroids in the middle of the twentieth century, the only effective drug treatments for inflammatory disease were a very few Nonsteroidal, Antiinflammatory Drugs (NSAIDs), aspirin, phenylbutazone, indomethacin and oxyphenbutazone [22]. Although the choice of this type of drug has widened, and the range of serious side-effects diminished since then, there is little evidence that such drugs are effective in PMR and they are not without significant risk in the elderly population that develops PMR [23, 24]. There are some reports of NSAIDs in the management of PMR before corticosteroids were introduced [25-27]. Very few patients get sufficient relief from the pain and stiffness of PMR with NSAIDs [6], and none of the newer drugs have challenged corticosteroids as the first-line treatment of choice in PMR. There are recent reports that NSAIDs do influence the radiological status of the joints, and perhaps the clinical outcome, in ankylosing spondylitis, when they are used in combination with a biological DMARD that inhibits TNF alpha. This may lead to a reassessment of NSAIDs in the therapeutics of rheumatic diseases [28]. In GCA the risk of using symptomatic treatments of this type in place of corticosteroids is much too great [6]. The risks of blindness and/or stroke, frequent complications of untreated GCA, are not diminished by the use of NSAIDs. Brawer in 2016 [29], reported treating PMR patients with NSAIDs and hydroxychloroquine with almost no use of corticosteroid. However, more than 80% of his patients initially presenting as PMR were subsequently considered to have seronegative rheumatoid arthritis.

Glucocorticoid Treatment: When Hench and his colleagues [30] isolated cortisol and demonstrated its remarkable anti-inflammatory effect, the efficacy of this hormone in alleviating the symptoms of PMR was rapidly recognized [25]. GCA was also shown to respond rapidly and reliably to corticosteroids [31]. As a result, over the past six decades, corticosteroids have been the treatment of choice for both of these conditions [32-35]. PMR is now recognized as the most common inflammatory disorder of the elderly, and PMR/GCA the most common reason for the prolonged use of corticosteroids in older adults [33,34]. It is the authors' belief that, despite the close association between PMR and GCA, these are separate disorders [22], and, for the purposes of this review, attempts have been made to focus on PMR. Many studies do not make this distinction, and where it is considered relevant these studies are included in the current analysis. Corticosteroids have long been known to have a high incidence of serious side-effects [24,36,37]. These cause greater morbidity in the elderly. Osteoporosis, rapid weight gain and new-onset, or significant loss of control, of diabetes mellitus are probably the most serious [37].

Other Historical Attempts at Drug Treatment

Dapsone: Dapsone is a sulphonamide antibiotic, effective in the treatment of leprosy that has immunosuppressive effects. It was introduced as a treatment for rheumatoid arthritis in the hope that it would be as effective as gold salts but with less toxicity [38,39]. A similar hope was held for its use in PMR and GCA [40,41]. Unfortunately, although it proved to be an effective DMARD, in both rheumatoid arthritis and PMR/GCA its toxic effects (haemolytic anaemia and agranulocytosis) made it unacceptable for long term control. Galeozowski, et al [42] tried another sulphonamide antibiotic, trimethoprim/sulphamethoxazole, in PMR without success.

Cyclosporin A: Cyclosporin A has been tried as a steroid sparing agent in GCA, but it was not effective [43,44].

Effects of Currently Used Dmards in PMR and GCA

Many of the DMARDs currently in use in chronic rheumatic diseases have been studied as possible ways to control PMR, and to reduce the exposure to corticosteroids.

Antimalarials: In 1983 David-Chaussee and his colleagues [45] reviewed 176 patients with PMR and GCA who had received treatment with NSAIDs and hydroxychloroquine after initiating treatment with corticosteroids. Only 5 of these subjects suffered a relapse of their symptoms. Other studies have supported this [46]. However, the long interval between exhibiting this drug and the onset of its antirheumatic effect, a minimum of 16 weeks of treatment, means that it is not very effective in reducing the amount of corticosteroid administered to these patients [47]. There are very few recent reports of antimalarial drugs being used in PMR, and Lee, et al [48] report it as worsening the outcome of the disease.

Methotrexate: When, during the last two decades of the twentieth century, methotrexate was shown to have major benefit as a Disease Modifying Anti-Rheumatic Drug (DMARD) in the management of chronic inflammatory rheumatoid arthritis [49, 50], similar benefit was sought in the treatment of patients with PMR. Overall, these efforts were not very successful.

Methotrexate alone has little effect on the pain and stiffness of PMR and what little beneficial effect it has, is not evident for about 10 -15 weeks after the onset of treatment during which almost all patients receive corticosteroid treatment [51]. Although a few studies found some benefit by reducing the dose of corticosteroid required to maintain the remission of symptoms, and/or the total dose of corticosteroid administered [36,52,53], others showed no benefit [54,55]. A similar lack of steroid-sparing was found in GCA [56,57]. Despite the lack of strong evidence supporting the use of methotrexate in PMR, EULAR and the ARC have suggested that methotrexate be considered as a corticosteroid sparing agent in PMR [58].

Azathioprine: Azathioprine was considered as a DMARD in the treatment of rheumatoid arthritis before the benefit of methotrexate became evident [49,50]. Although it is no longer preferred to methotrexate as a DMARD, De Silva and Hazleman [59] carried out a trial of this drug as a steroid sparing agent in PMR and GCA in 1986. This showed only a very marginal effect. Separate reviews by Salvarani, et al [60] and Spies, et al [55] concluded that azathioprine was ineffective in this regard.

Leflunomide: Leflunomide was developed as an immunosuppressive treatment for human allotransplants and then was used as an effective disease modifying anti-rheumatic drug in the management of rheumatoid arthritis beginning in the last decade of the twentieth century [61-63]. At that time its efficacy was proven but the mode of action was unknown. However, it has since been shown that the major active metabolite of leflunomide is an inhibitor of the enzyme dihydroorotate dehydrogenase [64] and thus it inhibits dendritic cell maturation and reduces the production of IL-6 from these cells [65]. Leflunomide has been investigated as a possible alternative to corticosteroids in the treatment of PMR and GCA. Initial reports were encouraging [66,67], but a high incidence of side-effects in addition to its very prolonged retention in the body after absorption [68], has not encouraged widespread use of this drug in this capacity [69].

Mycophenylate Mofetil: This immunosuppressant drug was introduced as an agent for organ transplantation [70]. Sciascia, et al [71] tried it as a steroid sparing agent in GCA and reported it as beneficial in three cases. In contrast, Banerjee and Brosnahan [72] in 2008, reported a patient immunosuppressed on mycophenylate mofetil following renal transplantation, who developed PMR while on this treatment.

Biological DMARDs

Since the work of Feldman and Maini [73] eliciting the biochemical and cytokine pathways involved in inflammatory responses, a burgeoning number of biological agents have been introduced into clinical practice with resulting beneficial effects in the control of inflammatory diseases [74], despite these agents also being implicated in the causation of some auto-immune, inflammatory conditions [75] such as interstitial lung disease caused by antagonists of TNF alpha, and SLE or vasculitis caused by other cytokine inhibitors [76,77]. PMR and GCA have been included in these studies.

Tumour Necrosis Factor-Alpha (TNF) Antagonists: Effective anti-inflammatory action in chronic rheumatoid arthritis using a number of TNF-alpha antagonists has been demonstrated [78-81]. As a result, the effect of these medications in the treatment of PMR/GCA was explored, especially to determine whether they might result in the use of lower dosage of corticosteroids, or less prolonged corticosteroid exposure. Initial studies in patients with PMR, using infliximab, a chimeric monoclonal antibody against TNF-alpha gave promising results [82-84], but subsequent studies showed no benefit from such treatment [85,86]. Initial experience with etanercept, an artificial soluble TNF-alpha receptor binding Fc fusion protein, was also promising [87]. The initial effect was to provide a modest reduction in the activity of PMR such as some alleviation of the symptoms and mild reduction of the erythrocyte sedimentation rate (ESR), but further studies show that the effect is limited and unlikely to prevent or reduce the exhibition of corticosteroids in PMR patients [88]. Watson and Gaston [89] and Seror, et al [90] reached a similar conclusion using adalimumab, a fully human monoclonal antibody to TNF-alpha. Gonzalez-Gay and his colleagues [91] concluded, in a review, that TNF alpha blockade was not indicated in the management of PMR.

B-Cell Depletion: B-cell depletion has proven effective in patients with rheumatoid arthritis, especially in those patients who are sero-positive for rheumatoid factor and/or anti CCP antibodies. However, there are no known autoantibodies specific to PMR or GCA and it seems unlikely that this would be an effective strategy for treating these patients. When tried, the outcome has not been encouraging.

Interleukin-1 blockade: Ly, et al noted that interleukin-1 beta is intimately involved in the inflammation of the affected arterial walls in GCA. They attempted to control GCA in three patients using the interleukin-1 blocking agent, anakinra without the use of corticosteroids. Anakinra is a recombinant human interleukin-1 antagonist. They observed improvement in the biomarkers for inflammatory disease, and in the symptoms of the arteritis in two of the three subjects studied. However, there is little or no additional evidence to support the use of this agent in PMR or GCA.

Interleukin-6 (IL-6) Blockade: IL-6 is a cytokine that is present abundantly in the synovium and the serum of patients with rheumatoid arthritis. It affects the function of T cells, B cells, monocytes and osteoclasts and is a major stimulant to the liver to produce acute phase proteins. Tocilizumab is a humanized monoclonal antibody that binds to the cell receptors for IL-6. It was first used as a treatment for rheumatoid arthritis in Japan. The Bologna group demonstrated that high levels of the serum IL-6 receptor combined with the presence of a low haemoglobin predicted relapse in PMR in both steroid treated and steroid naïve patients. Lally and his colleagues reporting a small open-label study of tocilizumab in PMR, noted that all patients achieved steroid-free remission at 6 months, and, in many, this lasted for 15 months. These included a few patients in whom corticosteroids were not exhibited. Toussirot and his colleagues

also considered IL-6 a suitable target for the treatment of PMR. 28 of 34 patients reported by this group achieved symptom-free remission and the remaining 6 reported significant symptom reduction. They did report a high incidence of serious side-effects including death from respiratory infection, but about 66 per cent remained in remission following discontinuation of the treatment. Similar results were reported. At present, tocilizumab represents the most promising agent for avoiding or reducing the side-effects of corticosteroids in elderly persons with PMR or GCA. However, tocilizumab has a high incidence of serious adverse effects, especially pyelonephritis and severe infections of the upper respiratory tract.

CONCLUSION

Despite the wide range of newer agents, both organic and biological, that have been introduced into the management of chronic inflammatory and rheumatic diseases over the past thirty years, none have proven sufficiently satisfactory as substitutes for corticosteroids in the treatment of PMR or GCA. Methotrexate and tocilizumab have been the most effective and their use can help reduce corticosteroid dosage and long-term use, but they are of limited benefit because of cost, and the frequency and severity of serious adverse effects. It is to be hoped that further agents under development will prove more effective or have fewer side-effects in achieving this goal.

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