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TOCILIZUMAB IN THE MANAGEMENT OF NEUROMYELITIS OPTICA SPECTRUM DISORDER: A NARRATIVE REVIEW OF LITERATURE AND CRITICAL APPRAISAL

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ABSTRACT

Background and objective:
Neuromyelitis Optica Spectrum disorder (NMOSD) mostly affects the spinal cord and optic nerves. This manuscript aims to explore the treatment potential of tocilizumab, a monoclonal antibody that targets the interleukin-6 (IL-6) receptor and regulates inflammatory cytokines implicated in the pathophysiology of NMOSD.

Methods:
A thorough search of the pertinent literature was done for this research utilising electronic databases, specifically PubMed, Cochrane Library, and Embase, which contained studies published from 2016 to 2024.

Results:
Clinical studies show that tocilizumab improves clinical outcomes and lowers recurrence rates in people with NMOSD, especially those who don't respond to traditional treatments. The medication's clinical utility is demonstrated by its capacity to lower MRI lesion activity, enhance Expanded Disability Status Scale (EDSS) ratings, and decrease annualised recurrence rates (ARR).

Conclusion:
Tocilizumab is a major step forward in the treatment of NMOSD, although further research may be required to ascertain its long-term safety and the most effective approach to utilise it for NMO spectrum illnesses.

Keywords: Neuromyelitis Optica Spectrum Disorder, Tocilizumab, IL-6 receptor, CNS Demyelinating diseases

INTRODUCTION

The central nervous system (CNS) is severely inflamed in neuromyelitis optica spectrum disorder (NMOSD), a chronic inflammatory disease that primarily affects the optic nerves and spinal cord. Due to distinct immunological mechanisms, such as the fact that over 80% of patients have aquaporin-4 immunoglobulin G antibodies (AQP4-IgG), it differs from multiple sclerosis (MS).[1,2] According to the International Panel for NMO Diagnosis, NMOSD is a condition linked to AQP4 autoimmunity and manifested by optic neuritis, acute myelitis, area postrema syndrome, and other central nervous system symptoms.[3]

Inflammation, demyelination, and tissue destruction are the outcomes of complement activation and immune cell recruitment brought on by AQP4-IgG binding to astrocytes in the pathophysiology of NMOSD.[4] Targeted immunotherapies, such as interleukin-6 (IL-6) receptor inhibitors, have recently broadened the therapy options for NMOSD.

An IL-6 receptor antagonist called tocilizumab has shown promise as a therapy for NMOSD. Tocilizumab decreases the generation of pro-inflammatory cytokines, lessens astrocyte damage, and helps avoid illness relapses by inhibiting IL-6 signalling.[5] The significance of targeted therapy in enhancing patient outcomes is shown by the approval of new medications, including eculizumab, inebilizumab, and satralizumab.[6,7] Notably, satralizumab, an IL-6 receptor inhibitor, was recently licensed by the U.S. Food and Drug Administration (FDA) to treat NMOSD in patients with and without AQP4-IgG, demonstrating its wide range of applications.[8]

Mechanism of Action

NMOSD pathophysiology is significantly influenced by IL-6 receptor signalling, which tocilizumab suppresses. IL-6 exacerbates CNS inflammation by encouraging B-cell differentiation and the generation of autoantibodies against AQP4. Astrocytic damage and demyelination are lessened by tocilizumab's inhibition of IL-6, which also lowers pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-17 (IL-17), and tumour necrosis factor-alpha (TNF-α).[9] Tocilizumab also reduces circulating B cells, which lowers the formation of autoantibodies and keeps NMOSD patients from relapsing.[10]

METHODS

To find publications published between 2016 and 2024, a thorough search of the PubMed, Cochrane Library, and Embase databases was conducted. "Neuromyelitis optica," "NMOSD," "Tocilizumab," and "IL-6 receptor" were among the keywords. Included were studies that examined the safety and effectiveness of tocilizumab in human subjects and were written in English.

In the beginning, 78 studies were found. Fifteen research, comprising observational studies, meta-analyses, and randomised controlled trials (RCTs), were chosen for evaluation after being screened for relevance. Clinical outcomes, relapse rates, and adverse events were the main focus of data extraction.

Five studies were critically appraised to assess the quality of evidence, and data were extracted on the study characteristics, including the sample size and intervention, the outcome measures, and the adverse effects.

RESULTS

Table 1 provides a summary of the studies that were part of this review.

Table 1: Summary of the included studies

Results					
Reference	**Pt: Group and Intervention**	**Type of Study**	**Outcome**	**Key Results & Findings**	**Study Weaknesses**
Manabu Araki (2018)	7 patients, 8mg/kg/4 weekly	Pilot study	Reduction in relapses, improved EDSS scores, and reduced neuropathic pain	ARR decreased from 2.9 ± 1.1 to 0.4 ± 0.8 ($p<0.005$), fatigue improved	Low sample size, treatment-related side effects
Marius Ringelstein (2019)	8 patients, retrospective	Observational study	Reduction in relapse rates	ARR decreased by 88.9%	Small cohort, adverse effects
Chao Zhang (2022)	108 patients (Tocilizumab vs Azathioprine)	TANGO trial (Phase 2 RCT)	Reduction in relapses compared to azathioprine	89% of the Tocilizumab group relapse-free compared to 56% in Azathioprine (HR 0.188, 95% CI 0.076-0.463)	Adverse effects in 36 out of 59 Tocilizumab-treated patients
Qin Fang Xie (2022)	89 patients, 8mg/kg/4 weekly	Meta-analysis	Most patients relapse-free	Effective and safe in NMOSD treatment	Drug-related adverse effects in 75 out of 89 patients
Carreón Guarnizo E (2020)	8 female patients, 6-8mg/kg/month	Observational study	Decrease in relapses and EDSS scores	Safe and effective	Side effects: hyperlipidemia, infections, DVT, small cohort

DISCUSSION

For NMOSD, tocilizumab has become a crucial treatment option, especially for patients who don't respond to traditional treatments. The medication's clinical utility is demonstrated by its capacity to lower MRI lesion activity, enhance Expanded Disability Status Scale (EDSS) ratings, and decrease annualised recurrence rates (ARR). With relapse-free rates of 89% in the tocilizumab group and 56% in the azathioprine group, randomised controlled trials (RCTs) like the TANGO study have shown its superiority over traditional medications like azathioprine.[11-13]

Clinical Trials:

Several clinical trials have confirmed the effectiveness of tocilizumab:

- Manabu Araki research (2018): Seven patients participated in pilot research that demonstrated a decrease in neuropathic pain, an improvement in EDSS scores, and an ARR of 0.4 [9,10].
- TANGO Trial (2022): This Phase 2 randomised controlled trial examined 108 patients and compared cilizumab and azathioprine. With 89% of patients remaining relapse-free, the tocilizumab group showed considerably decreased relapse rates.[11]
- Qin Fang Xie Meta-analysis (2022): Tocilizumab was shown to be safe and effective in 89 patients, with the majority of them avoiding relapses.[12]

Safety Profile:

Tocilizumab has some negative side effects despite its effectiveness:

- Infections: 36 of the 59 patients in the TANGO trial had infections, which calls for careful observation.[11]
- Observational studies have identified hyperlipidaemia and deep vein thrombosis, underscoring the necessity of all-encompassing patient care.[13]
- Elevation of liver enzymes: a frequent adverse event that has been documented in several investigations.[14]

In contrast, satralizumab, another IL-6 receptor antagonist, and eculizumab, a complement inhibitor, are alternative FDA-approved treatments for NMOSD. Although eculizumab has demonstrated a high level of effectiveness in preventing relapses, the danger of meningococcal infections and its expensive cost limit its use.[15,16] Satralizumab, on the other hand, is a desirable first-line treatment since it has a good safety record and lower risks of serious infections than other treatments.[17]

Table 2 provides a comparative overview of approved therapies for NMOSD:

Table 2: Comparative Overview of NMOSD Therapies

Therapy	Mechanism of Action	Key Clinical Trials	Safety Profile	Limitations
Tocilizumab	IL-6 receptor blockade	TANGO, observational studies	Infections, liver enzyme elevation	Monitoring required, adverse effects
Eculizumab	Complement inhibition	PREVENT trial	Risk of meningococcal infections	High cost
Satralizumab	IL-6 receptor blockade	SAkuraSky, SAkuraStar	Favorable safety profile	Limited data in AQP4-IgG-negative patients

Long-term research on tocilizumab's safety and effectiveness is necessary despite its potential. Unresolved issues include combination treatments, the best dosage, and its function in AQP4-IgG-negative patients.[18] To improve treatment algorithms and determine tocilizumab's place among currently available treatments, more comparison studies are necessary.

CONCLUSION

Tocilizumab is a viable treatment alternative for NMOSD, especially for those who don't respond to traditional treatments. Even though its effectiveness in lowering relapses and enhancing therapeutic results is well-established, more research is required to determine the best dosage schedules and long-term safety. A major development in targeted immunotherapy, the use of IL-6 receptor inhibitors such as tocilizumab in the treatment of NMOSD has the potential to revolutionise the therapeutic environment. Its use highlights the transition to precision medicine by guaranteeing that therapies are customised to the immunological profiles of individual patients. Tocilizumab's acceptance as a conventional treatment, however, is contingent upon thorough longitudinal

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