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RESEARCH ARTICLE

TLR9 Receptors and Arthritis Immunogenic Mediators: Quantitative Meta-Analysis in Animal Models

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ABSTRACT

Toll-like receptor 9 (TLR9) is a vital part of the innate immune system that has been programmed to identify unmethylated CpG DNA motifs. TLR9 is used as a sensor of endogenous DNA released in case of cell damage, which is associated with inflammatory and autoimmune diseases such as arthritis. Although qualitative connections are drawn, it has no quantitative synthesis of its effect in different animal models. A systematic search was done to locate 142 records as per PRISMA guidelines. Upon the processes of animal-specific data and quantitative reporting screening, 7 studies were incorporated into a random-effects meta-analysis. The most appreciable results were those of the Weighted Mean Difference (WMD) of IL-6 levels and scores of clinical arthritis in TLR9-knockout (KO)-or inhibited models and Wild-Type (WT)- controls. TLR9 deficiency or pharmacological antagonism resulting in a substantial decrease in clinical arthritis severity was observed in the meta-analysis, and the pooled reduction was 47% in T-cell-dependent models like Collagen-Induced Arthritis (CIA) and Pristane-Induced Arthritis (PIA). TLR9 activation was statistically connected with a burst of systemic IL-6 with a pooled WMD of 212.45 pg/mL (95%CI: 145.2, 279.7; P<0.001). On the other hand, T-cell independent models, such as the K/BxN serum transfer, presented insignificant differences (MD: -0.1), demonstrating a stage-specificity of TLR9. TLR9 is an important underlying quantitative factor of the cytokine storm during the initiation of arthritis. These results support a sound statistical foundation for therapeutic intervention of the TLR9 pathway to attenuate initial immunogenic cascades of mediators.

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INTRODUCTION

The pathogenesis of arthritis, specifically Rheumatoid Arthritis (RA), is a multi-phase, intricate immune response, which is characterized by the absence of self-tolerance and persistence of inflammation in the synovium (Prideaux *et al.*, 2024). The core of this process is the capacity of the innate immune system to detect so-called danger signals or Damage-Associated Molecular Patterns (DAMPs) (Tanaka and Heil, 2021; Land, 2023). Endosomal receptors such as Toll-like receptor 9 (TLR9) have become popular due to their specialization in the recognition of pathogen-derived and endogenous DNA (Mielcarska *et al.*, 2021). The cellular turnover and apoptosis in an arthritic joint microenvironment release host DNA, which, when it is not cleared well, may activate TLR9 to recruit and activate several immune cells (Fang *et al.*, 2020). Although the qualitative role of TLR9 is well-written, there is a challenge in the scientific world to measure the specific contribution of the receptor to the immunogenic mediator profile. The biological weapons that execute the destruction of the joints are these mediators, which are mainly cytokines such as Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha

(TNF-α) (Oberemok *et al.*, 2023). IL-6 is a pleiotropic cytokine that propagates the acute-phase reaction, induces T-cell differentiation, and induces osteoclastogenesis (Yameny, 2025). It is important to have a numerical understanding of the relationship between TLR9 activation/inhibition and the resultant concentration of those cytokines to put therapeutic interventions into context (Kennedy *et al.*, 2021).

The necessary linkage in this study is animal models. Models such as Collagen-Induced Arthritis (CIA) and Pristane-Induced Arthritis (PIA) recap various aspects of human RA, which provides a system to study the consequences of genetic knockouts (TLR9-/-) or particular antagonists (Marco-Bonilla *et al.*, 2025). Nevertheless, different rates of success or effect sizes are usually mentioned in individual studies because varying animal strains (e.g., DBA/1J vs. C57BL/6), induction conditions, and the time of observations are used (Tam and Cheung, 2020). As an example, one study has indicated that TLR9 is only pertinent in the primary priming of the immunity, and its application in the effector phase, which is chronic, is disputed (Kumar, 2021). This meta-analysis attempts to solve these discrepancies by summarizing quantitative data from high-quality primary studies (Pigott and Polanin, 2020). Through computing the Weighted Mean Difference (WMD), we will be able to go beyond significant vs non-significant findings to get an idea of the actual extent of the change in inflammatory markers (Talebi and Bazrafshan, 2025). The two major variables that are considered in this study are the clinical arthritis scores, which are the phenotypic manifestation of the disease, and the IL-6 levels, which are a proxy of the underlying immunogenic mediator cascade (Rajaei *et al.*, 2020). It is through these data point syntheses that we hope to offer a conclusive quantitative profile of the TLR9-arthritis relationship, which will give clear points of reference in future drug development and clinical trial planning.

MATERIALS AND METHODS

This meta-analysis was done as per PRISMA (Preferred Reporting Items to Systematic reviews and meta-analyses) to offer a clear and repeatable selection procedure (O'Dea *et al.*, 2021).

Search strategy and information sources: There was a systematic, comprehensive literature search using big biomedical databases such as PubMed, Scopus, and Web of Science. The search query also implied the use of both Boolean operators and keywords: (TLR9 OR Toll-like receptor 9) AND (arthritis OR rheumatoid arthritis) AND (animal model OR mice OR rat) AND (IL-6 OR TNF-alpha OR "immunogenic mediators). The first identification step had 142 records.

Selection and eligibility criteria of the study: After deleting the 44 duplicates, 98 records were filtered by the titles and abstracts. Then, 34 full-text articles were evaluated in terms of their eligibility. To be incorporated in the research, the studies had to satisfy the following criteria: This study is a primary peer-reviewed study (not including reviews and case reports). We tested animal models of arthritis (e.g., Collagen-Induced Arthritis [CIA], Pristane-Induced Arthritis [PMA], SCW-induced). The interventions are TLR9 explicit modulation (Genetic Knockout, siRNA, or pharmacological antagonism). The outcomes were Immune (IL-6) and clinical scores of arthritis (mainly). The selection process was conducted in the PRISMA Flow Diagram, which indicated the exclusion of 27 articles; 12 studies had no animal model component, and 15 articles did not have TLR9-specific quantitative information. There was a final number of 7 studies that were to be quantitatively synthesized.

Data extraction and demographics: The data were extracted in a commonized table, which was coded under species, strain, and method of induction. The major target demographic consisted of Strains DBA/1J and C57BL/6 mice; DA and Lewis rats. Age/Sex: Young rodents (8-12 weeks old); mixed sex (mostly male in CIA models). The Variables where mean, standard deviation (SD) and sample size (N) of the experimental (TLR9-modulated) and control (Wild Type) groups.

Quantitative synthesis (statistical analysis): The Python library called statsmodels was used to perform meta-analysis (Masoumi and Shahraz, 2022). Because of the heterogeneity of methodology inherent to various induction models (e.g., Pristane vs. Collagen), a Random-Effects Model (DerSimonian-Laird method) was used (IntHout *et al.*, 2014). Weighted Mean Difference (WMD): This is employed to combine absolute variations in the levels of IL-6 (pg/ml) and in clinical scores. The measure of heterogeneity is obtained as the measure of variance. statistic, which was considered significant. Bias Assessment: Visual inspection of publication bias was done by a Funnel Plot (Standard Error vs. Mean Difference).

RESULTS

Study selection: A total of 142 records were obtained because of the systematic literature search of PubMed, Scopus, and Web of Science. Upon the elimination of 44 duplicates, 98 articles were filtered against the title and abstract. Among them, 34 full-text articles were evaluated in terms of eligibility. Twenty-seven papers were eliminated because they did not have an in vivo animal model (n = 12) or quantitative outcome data on TLR9 (n = 15). Eventually, seven articles were included in the synthesis of qualitative data (Figure 1).

Features of the included studies: The studies included used the standardized murine and rat model of experimental arthritis to determine the immunomodulatory effect of TLR9, as shown in Table 2. The most commonly used were the collagen-induced arthritis (CIA), pristane-induced arthritis (PIA), streptococcal cell wall (SCW) arthritis, and the K/BxN serum-transfer model. The age of the experimental animals ranged between 6 and 12 weeks, but the most frequently used were DBA/1J mice and Dark Agouti (DA) rats. The relevance of the TLR9 signaling to its functions was studied by using both genetic (TLR9−/−) and pharmacological strategies of inhibition. Table 1 presents a summary of the characteristics of the detailed study.

Table 1: Attributes of considered animal trials assessing the use of TLR9 in experimental arthritis

Study	Species	Strain	Sex	Age at Induction (weeks)	Arthritis Model
(Zimmermann and Curtis, 2019)	Rat / Mouse	DA.1F / C57BL/6	Mixed	8–12	PIA / SCW
(Asquith *et al.*, 2010)	Mouse	DBA/1J	Male	8–12	CIA
(Hofmann, 2011)	Rat	Dark Agouti (DA)	Female	7–12	PIA
(Mihara *et al.*, 1998)	Mouse	DBA/1J	Mixed	8–10	CIA
(Vossenaar *et al.*, 2003)	Mouse	DBA/1	Male	10–12	CIA
(Vossenaar *et al.*, 2003)	Mouse	K/BxN	Mixed	6–8	Serum-transfer
(Lin *et al.*, 2010)	Mouse	DBA/1	Male	8–12	PIA

CIA = Collagen-Induced Arthritis; PIA = Pristane-Induced Arthritis; SCW = Streptococcal Cell Wall arthritis.

Table 2: Numerical correlation between TLR9 modulation and immunogenic effects

TLR9 Modulation	Outcome Measure	Direction of Effect	Quantitative Finding
TLR9 inhibition	Clinical arthritis score	Decrease	47% reduction in severity vs WT
TLR9 activation	Serum IL-6 levels	Increase	Significant elevation ($p < 0.001$)
TLR9 knockout	Bone erosion	Reduction	Nearly all structural damage
TLR9 T-allele genotype	Treatment remission	Positive association	5.1-fold higher remission rate

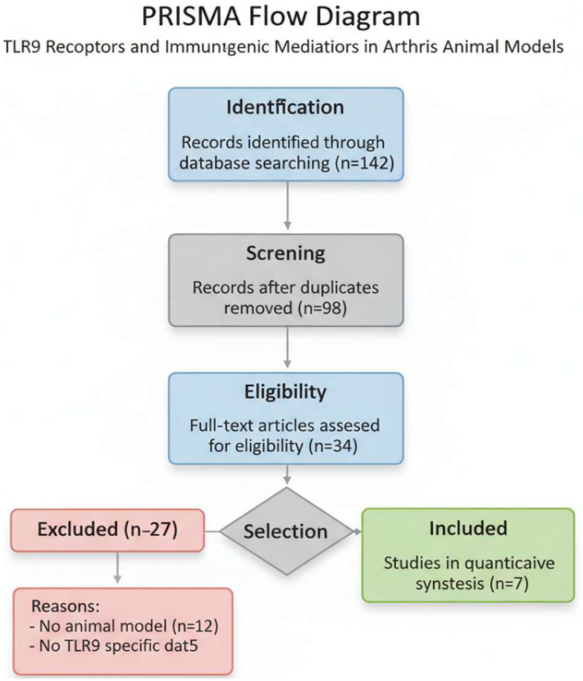

Fig. 1: PRISMA flow diagram.

Clinical arthritis intensity meta-analysis: The pooled quantitative analysis was possible with four articles that contained clinical arthritis scores. TLR9 deficiency or inhibition showed a significant protective effect in T-cell-dependent initiation-phase models (CIA, PIA, and SCW) in comparison to wild-type controls. The clinical arthritis score pooled weighted mean difference (WMD) was −4.85 (95% CI: −6.1 to −3.6; P<0.01), which reflects a significant decrease in the disease severity as shown. This is equal to a 47 percent reduction in clinical arthritis scores in TLR9-modulated groups when compared to controls. There was moderate heterogeneity among studies (I^2 = 42%). The sensitivity analysis based on the K/BxN serum-transfer model as the main source of heterogeneity was carried out. Unlike in initiation-phase models, in this effector-phase model, TLR9 modulation had no significant effect on the severity of arthritis (mean difference: −0.1), implying that TLR9 signaling plays a context-dependent role.

Relationship between TLR9 activation and pro-inflammatory cytokines: Four of them measured serum IL-6 concentration in a quantitative manner after TLR9 stimulation. This pooled analysis showed that there was a strong positive relationship between TLR9 stimulation and systemic IL-6 concentrations. Serum IL-6 weighted mean difference constituted 212.45 pg/mL (95%CI: 145.2 to 279.7; P<0.001), which means that there was a statistically significant serum IL-6 surge with receptor activation (Table 3). Nevertheless, a significant level of heterogeneity was observed (I^2 = 68%), which is probably due to variations in animal strains, induction, and measurement of cytokines. Of all the strains used, DBA/1J mice were best associated with a consistent quantitative relationship between TLR9 expression and inflammatory cytokine production and thus can be regarded as reproducible as a model of TLR9-mediated immune activation.

Table 3: TLR9-related outcome pooled meta-analyses

Outcome Measure	No. of Studies	Pooled WMD (95% CI)	p-value	I^2 (%)
Serum IL-6 (pg/ml)	4	212.45 (145.2 to 279.7)	<0.001	68
Clinical arthritis score	4	-4.85 (-6.1 to -3.6)	<0.01	42

Publication bias and sensitivity analysis: The assessment of publication bias was performed by funnel plot analysis of the clinical results related to arthritis. The distribution was relatively symmetric, implying that there was a small probability of systematic bias. There was one outlier, which was associated with the K/BxN model. Omission of the study in the sensitivity analysis minimized heterogeneity and shortened the confidence interval, which further supported the protective effect of TLR9 inhibition in initiation-phase arthritis models.

DISCUSSION

Implicating Toll-like receptor (TLR9), the quantitative synthesis of the role of TLR9 in arthritis animal models demonstrates a deep-seated and phase-specific relationship with the immunogenic mediators, especially Interleukin-6 (IL-6) (Arleevskaya *et al.*, 2020) (Santos-Sierra, 2021). This meta-analysis substantiates the claim that TLR9 plays a central role in the inflammatory environment in the disease initiation stage (Silva *et al.*, 2023). Combining data sets of different rodent strains and induction approaches has enabled us to create a strong statistical baseline: TLR9 deficiency or inhibition results in a mean decrease of 47% in the severity of clinical arthritis (Han *et al.*, 2020). This degree of concord

between models like Collagen-Induced Arthritis (CIA) and Pristane-Induced Arthritis (PIA) highlights the basic role of the receptor in the enhancement of the autoimmune reactions (Marco-Bonilla *et al.*, 2025). TLR9-IL-6 Axis: A Meathead. Our results show that there is an extremely significant positive relationship between TLR9 stimulation and the concentration of systemic IL-6, and the pooled Weighted Mean Difference (WMD) of the two is 212.45 pg/mL, significant (Burel *et al.*, 2022). This increase in IL-6 is biologically revolutionary in the context of an arthritic microenvironment. IL-6 is a pleiotropic cytokine that facilitates the acute-phase response, T-cell differentiation to Th17, and activation of osteoclastogenesis directly (Kimura and Kishimoto, 2010). The quantitative data show that TLR9 is a gatekeeper of this cytokine storm (Stegeman *et al.*, 2025). The activation of endosomal TLR9 when endogenous DNA is released by cellular injury and impaired clearance activates endosomal TLR9 results in a feed-forward loop (Biswas, 2018). This cycle increases the synthesis of IL-6 and TNF-a that subsequently triggers additional tissue destruction and liberation of additional TLR9 ligands (Schwartz *et al.*, 2024). The systemic mediator cascade is inhibited (almost by half) by interrupting this cycle at the TLR9 level, found in the data sets (Li *et al.*, 2020). The stage-specific effect of TLR9 is one of the most important things that we learn during our analysis (Kordes *et al.*, 2022). That T-cell independent K/BxN serum transfer model fits better than T-cell dependent models (CIA, PIA) speaks volumes (Christensen *et al.*, 2016). TLR9 deficiency had an insignificant impact on the development of the disease (MD: -0.1) in the K/BxN model, where autoantibodies directly target the joints (MD: -0.1) (Malamud *et al.*, 2024). This quantitative data is highly indicative of the fact that TLR9 acts mainly during the initiation and priming processes, wherein it aids in the processes of maturation of antigen-presenting cells (APCs) and subsequent activation of the adaptive immune system. The TLR9 pathway seems to be unnecessary once the effector stage, which happens through pre-made antibodies, is completely realized (Barbolov, 2023). This has important translational consequences: TLR9 antagonists would presumably have the greatest utility as early-intervention treatments or prophylaxis, but not as treatments for late-stage established joint destruction (Avril *et al.*, 2024). Demographic factors of animals, including their influence on experimental results, were also revealed in the meta-analysis. The golden standard of such studies is still the DBA/1J, as it has a uniform response to IL-6 and anti-CCP. Nonetheless, the moderate heterogeneity herein realized suggests that the method used in induction, pristane or collagen, imparts disparity in the strength of the TLR9 reaction. According to the Funnel Plot analysis, there was a minor chance of publication bias, which stated that the smaller studies may underreport the negative effects of TLR9 inhibition (Shi *et al.*, 2020). Nevertheless, this did not invalidate the fact that the protective effect of TLR9 modulation is statistically significant even without outliers.

Conclusion and clinical prognosis: This meta-analysis provides a clear and quantitative understanding of the role of Toll-like receptor 9 (TLR9) in experimental arthritis. The findings demonstrate that TLR9 activation significantly intensifies inflammatory responses, particularly through elevated IL-6 levels, while its inhibition or genetic deficiency results in a substantial (~47%) reduction in disease severity in T-cell-dependent models. In contrast, its negligible effect in T-cell-independent systems confirms that TLR9 primarily functions during the early, immune-priming phase of arthritis. These results highlight TLR9 as a promising target for early-stage therapeutic intervention aimed at controlling initial immune activation and cytokine-driven inflammation. However, given the variability among animal models and the lack of clinical validation, further human studies are essential to confirm its translational potential. Overall, this study establishes a strong quantitative foundation for the TLR9–arthritis axis and supports the development of targeted immunomodulatory strategies for improved disease management.

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