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# IgA Nephropathy: Insights into Genetic Basis and Treatment Options

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*In memoriam of Prof. Efsthios Alexopoulos*

## 1. Introduction

IgA nephropathy (IgAN), is the most common primary glomerulonephritis worldwide. On light microscopy the picture can vary from slight mesangial hypertrophy to extra capillary proliferation of glomeruli, with sclerosis and interstitial fibrosis. On immunofluorescence staining of kidney sections the disease is characterized by mesangial deposits of IgA, predominantly polymeric IgA (pIgA) of the IgA1 subclass, and often co-deposition of complement factor C3, properdin and IgG. It is important however to realize that, although IgA mesangial deposits are necessary for the diagnosis of IgAN, the latter is not obligatory in every individual with mesangial IgA deposits. Thus, IgA deposits may also be seen in subjects with no evidence of renal disease [Suzuki et al, 2003; Waldherr et al, 1989] at an incidence that ranges from 3 to 16 percent. Furthermore, there are also a number of reports documenting IgA deposition in other forms of glomerulonephritis, particularly thin basement membrane disease, lupus nephritis, minimal change disease, and diabetic nephropathy, a finding which is most probably casual rather than causal.

IgAN occurs at any age, but most commonly the age of onset is in the second or third decade of life. Males are more often affected than females, with a male:female ratio of 2:1. Most patients with IgAN present microscopic hematuria with or without mild proteinuria. About 40% of patients have episodes of macroscopic hematuria. This is sometimes preceded by infections, most commonly upper respiratory tract infections, a phenomenon known as “synpharyngitic” hematuria. Other infections like gastrointestinal or urinary tract infections have also been reported to precede macroscopic hematuria. Proteinuria is common and can vary from mild proteinuria to nephrotic syndrome.

IgAN has been considered a benign disease for a long time, but nowadays it is clear that 30-40% of patients may develop renal failure with significant socioeconomical consequences. In Western Europe and the United States of America 7-10% of the patients on renal replacement therapy suffer from IgAN. The severity of histological lesions, especially diffuse proliferative glomerulonephritis, marked capsular adhesions, fibrocellular crescents, glomerular hyalinosis and severe sclerosis, as well as tubulointerstitial damage correlate

with poor renal outcome [Skena, 1998]. Next to the gravity of histological lesions, unfavourable outcome is associated with persistent hematuria and proteinuria of more than 1g/day, decreased glomerular filtration rate (GFR) at the time of the diagnosis, and hypertension. Although several laboratory tests have been reported to correlate with clinical outcome, so far no reliable biomarker has been identified to predict outcome in IgAN. Recurrence of IgAN after renal transplantation is common. This finding, along with the observation that IgA depositions disappear from a kidney of an IgAN patient, after transplantation of this kidney to a non IgAN patient, are suggestive of a rather systemic disease.

## 2. Genetics of IgAN

The strongest evidence for the existence of genetic factors in the development and/or progression of IgAN comes from descriptions of familial IgAN, largely in white populations [Julian et al, 1985], and recent studies suggest that familial and sporadic IgAN may share a common pathogenic mechanism and similar outcomes [Izzi et al, 2006]. The genetic predisposition may be independent of environmental factors and may reflect an inherited susceptibility to develop mesangial glomerulonephritis.

IgAN does not exhibit classic single-gene Mendelian inheritance pattern [Frimat & Kessler, 2002]. The complex genetic pattern of IgAN is reflected by the multiple pathways involved in its immunopathogenesis, namely multiple discrete immunologic abnormalities related to the abnormal overproduction and release of mucosal pIgA1 in the systemic compartment and possibly other protein functional abnormalities related to a propensity for mesangial deposition of pIgA1. It is therefore probable that the disease-associated genetic variations at identified *IGAN* loci, instead of occurring in the form of “classic” nonsense/missense/splice site mutations and deletions/insertions that affect protein structure and function, may be rather of the type specific single-nucleotide polymorphism (SNP) alleles in non-coding regions or synonymous SNPs in coding regions. The latter function as *cis*-acting elements that alter the transcriptional activity of a disease gene and/or messenger RNA stability and, therefore, the expression level of the encoded protein. It is interesting that recent studies indicate that 30% to 50% of human genes with coding SNPs can present allelic variation in gene expression [Hoogendoorn et al, 2003; Lo et al, 2003]. From this point of view, the most comprehensive theory is that several genetic loci contribute significantly to the disease susceptibility that underlie the primary immunologic defects observed in IgAN. Each locus may occur at a different prevalence rate in different racial/ethnic groups. Variations at these major genetic loci may not be sufficient for the development and progression of IgAN and the contribution from a potentially large number of modifying genes with modest genetic effects but high prevalence is probably needed as well. The various allelic combinations of these loci may underlie the different disease phenotypes (disease development and progression, nephritic vs. nephrotic clinical presentation, histopathologic subclass, severity of disease, responsiveness of proteinuria to angiotensin-converting enzyme [ACE] inhibitors and/or angiotensin II receptor blockers [ARBs], etc.) observed in IgAN. For diseases with complex genetic pattern, it has been shown that the optimal analysis approach is the combination of linkage, association and sequence approaches. Until now, two basic approaches have been used in genetic studies of IgAN: a) genome-wide linkage analysis study, a methodology that has been used successfully to identify major disease/susceptibility loci, b) candidate-gene association study, mainly used to identify

altered genes with modest genetic effects but high prevalence. Recently, a genome-wide association study was carried out in cohorts of Chinese and European IgAN patients (A.G.Gharawi et al, 2011). Five loci (3 in the major histocompatibility complex at chromosome 6p21, a common deletion of CGHR1 and CFHR3 at chromosome 1q32 and one locus at chromosome 22q12) were identified. They explain 4-7% of the disease variance.

## 2.1 Genome-wide linkage analysis studies

Genome-wide linkage analysis is used successfully to identify major disease/susceptibility genes but has limited power to detect genes of modest effect. Linkage studies involve recruitment of families with multiple affected individuals. In a typical whole-genome linkage scan, up to 400 microsatellites, or equivalently approximately 10,000 SNP markers, equally spaced across the genome, are typed in families to interrogate marker cosegregation with a disease phenotype. The advantage of genome-wide linkage studies is that they do not require a priori assumption about disease pathogenesis. These studies are very sensitive to phenotype misspecification, however their power is limited to detecting rare genetic variants with a relatively large effect on the risk of disease.

Linkage studies of IgAN are faced with multiple challenges. Familial forms of IgAN are frequently underrecognized because the associated urinary abnormalities in affected family members are often mild or intermittent. Moreover, once familial disease is documented, systematic screening by renal biopsy cannot be justified among asymptomatic at-risk relatives, necessitating reliance on less accurate phenotypes, such as microscopic hematuria, to diagnose affection. Additionally, IgAN has been observed to co-occur in families with thin basement membrane disease (TBMD), an autosomal dominant disease caused by heterozygous mutations in the collagen type IV genes (COL4A3/COL4A4) [Frasca et al, 2004]. Short of kidney biopsy or direct sequencing of the very large collagen genes, TBMD cannot be reliably excluded among relatives of IgAN patients. Finally, because urinary abnormalities may manifest intermittently, one also cannot unequivocally classify at-risk relatives as unaffected, necessitating affected-only linkage analysis. The inability to classify affected and unaffected individuals accurately is commonly encountered in linkage studies of complex traits, leading to decreased study power. Increasing sample size by including additional families is also not necessarily helpful in these situations because the diagnosis of IgAN likely encompasses several disease subsets, such that expansion to larger sample size can paradoxically reduce analytic power due to increased heterogeneity [Durner et al, 1992; Cavalli-Sforza & King, 1986].

To date, four genome-wide linkage studies of familial IgAN have been reported [Gharavi et al, 2000; Bisceglia et al, 2006; Paterson et al, 2007, Feehally et al, 2010]. Families in these studies have all been ascertained via at least two cases with biopsy-documented IgAN, with additional family members diagnosed as affected based on clinical evidence (renal failure or multiple documentation of hematuria/proteinuria). In the first study, 30 families with two or more affected members were examined [Gharavi et al, 2000]; multipoint linkage analysis under the assumption of genetic heterogeneity yielded a peak LOD score of 5.6 on chromosome 6q22-23 (locus named IGAN1), with 60% of families linked. The remainder of families linked to chromosome 3p24-23 with a suggestive LOD of 2.8. This study demonstrated that IgAN is genetically heterogeneous but argued for the existence of a single locus with a major effect in some families. In the second genome-wide linkage study 22 Italian IgAN families were enrolled [Bisceglia et al, 2006] (see section 2.3). The third linkage

scan was based on a unique large pedigree with 14 affected relatives (two individuals with biopsy defined diagnosis and 12 with hematuria/proteinuria on urine dipstick) [Paterson et al, 2007]. Linkage to chromosome 2q36 was detected with a maximal multipoint LOD score of 3.47. Most reported linkage intervals did not contain obvious candidate genes, but the 2q36 locus encompasses the COL4A3 and COL4A4 genes, which are mutated in TBMD. Together with the high penetrance of hematuria, this finding suggests that affected individuals in the 2q36-linked family may belong to an IgAN subtype that overlaps with TBMD. Finally, the fourth genome-wide analysis, carried out in a cohort of IgAN patients selected from the UK Glomerulonephritis DNA Bank, the region of the MHC (major histocompatibility complex). The strongest association signal included a combination of DQ loci and HLA-B. This study suggests that HLA region contains some alleles that predispose to the disease in the UK population. In conclusion, four genome-wide linkage studies, carried out in four different IgAN patient populations, demonstrate different chromosomal traits linked to the disease.

None of the genes underlying these linkage loci has been identified until now. The underlying reasons are numerous, including the phenotyping difficulties discussed above; the presence of locus heterogeneity, which limits the ability to precisely map the disease interval and find additional linked families to refine loci; the contribution from non-coding susceptibility alleles (e.g. point mutations or structural genomic variants within intronic or promoter regions), which usually escape detection if mutational screening is confined to exonic regions. It is expected that the availability of inexpensive Next-Gen sequencing will enable comprehensive interrogation of linkage intervals, facilitating identification of disease-risk alleles.

In addition, future studies of this kind that aim at dissection of increasingly genetically homogeneous cohorts must consider the importance of defining distinct clinical subtypes of IgAN that may exist within the single pathologic ascertainment criterion currently used to diagnose IgAN: light microscopic evidence of mesangial deposits of IgA by immunofluorescence. As with all family-based genetic studies, there is a high degree of dependency on access to sufficient numbers of clinically well-phenotyped and genetically informative cohorts. To address the paucity of cohorts with biopsy-proven IgAN available for the conduct of linkage-based, association-based, and sequence-based approaches, the European IgAN consortium has published the details of its IgAN Biobank resource [Schna et al, 2005].

## 2.2 Candidate-gene association studies

Candidate-gene association studies examine polymorphisms in only specific genes that are selected based on a priori assumption about their involvement in the disease pathogenesis, and they are highly sensitive to population stratification, multiple testing, and reporting bias. As a result, most candidate-gene association studies in the literature have not been replicated [Ioannidis et al, 2001; Hsu SI et al, 2000; Hsu SI, 2001; Frimat & Kessler, 2002], an issue which questions the validity and the methodology used in these studies [Hsu & Feehally, 2008]. Not surprisingly, candidate-gene studies for IgAN have also been largely unrevealing. Many candidate genes have been proposed, but for most of them no solid a priori evidence for their involvement in IgAN existed, whereas most were studied in the context of IgAN progression rather than causality. Over the last 15 years, there were more than 120 candidate-gene association studies for IgAN published in the English literature and



indexed on PubMed (e.g., components of the renin-angiotensin-aldosterone pathway, mediators of inflammation and/or vascular tone, components of the mesangial matrix, and various receptors for polymeric IgA1 expressed in mesangial cells) [Kirylyuk et al, 2010]. Of these, 39 (31%) studies examined genetic polymorphisms in association with susceptibility to IgAN, 40 (32%) examined an association with disease severity, progression, or complications, and 44 (35%) examined both susceptibility and risk of progression. Many candidate-gene association studies are lacking in functional genetics.

Approximately one third of all studies involved polymorphisms in the renin-angiotensin-aldosterone system (RAAS). A widely studied example of the dilemma of repeated non-replication of results is represented by genetic case-control association studies of the angiotensin I-converting enzyme (*ACE*) gene insertion/deletion (I/D) polymorphism in the development and/or progression of IgAN, as well as a whole host of common human diseases and conditions, including cardiovascular disease, complications of diabetes such as retinopathy and nephropathy, glomerular, tubulointerstitial, and renal cystic renal diseases, and even renal allograft survival [Hsu SI et al, 2000; Hsu SI, 2001; Schena et al, 2001]. The interest in studying the *ACE* I/D polymorphism is based on evidence for “biologic plausibility.” Rigat and colleagues reported in 1990 that the *ACE* I/D polymorphism in intron 16 of the human *ACE* gene accounts for half of the variation in serum *ACE* levels in a white study cohort [Rigat et al, 1990], and this is due to the presence of a transcriptional repressor element in the I allele [Hunley et al, 1996].

There have been numerous population-based studies that either support or refute an association between the D allele and progression of renal disease in these conditions [Hsu SI et al, 2000; Hsu SI, 2001]. Recent meta-analyses have concluded that the D allele is not associated with renal disease progression in patients with IgAN or diabetic nephropathy [Schena et al, 2001; Kunz et al, 1998]. Despite more than a dozen generally small genetic case-control studies of the *ACE* I/D polymorphism in both white and Asian IgAN cohorts have been done, no definite conclusions can be drawn from them regarding the association between the D allele or DD genotype and development and/or progression of IgAN. Population-based genetic association studies of other genes encoding proteins in the RAAS such as angiotensinogen (*AGT*) and the angiotensin II type 1 receptor (*ATR1*), as well as renin (*REN*) and aldosterone synthase (*CYP11b2*), have also generated conflicting results, as have similar studies of the “expanded” RAAS that includes 11b-hydroxysteroid dehydrogenase type 2 (*11bHSD2*) and the mineralocorticoid receptor (*MLR*) [Poch E et al, 2001]. In general, the approach has been to genotype a single common polymorphism in each gene with the use of polymerase chain reaction/restriction fragment length polymorphism (PCR-RFLP). It is remarkable that to date, the role of the RAAS, whose components *ACE* and *ATR1* are the targets of *ACE* inhibitors and angiotensin-II receptor blockers (ARB), respectively, has not been convincingly demonstrated by any genetic association study.

In general, most of these studies were of poor quality and severely underpowered and, therefore, negative findings were almost universally inconclusive. Overall, the average size of case-control cohorts per study was 182 cases and 171 controls. Many studies used ad hoc controls derived from unscreened blood donors who were poorly matched to the cases in terms of ancestry and geography. The potential impact of confounding by population stratification was ignored by the majority of studies, despite the fact that the tools for quantification of this problem have been developed. An additional matter of concern is the

lack of adequate correction (permutation testing) for multiple, non-independent tests which would be anticipated as long as several of these studies tested several hypotheses (multiple polymorphisms, multiple phenotypes, or multiple genetic models). Other major problems included inadequate or variable SNP coverage of candidate genomic areas, with several studies examining only a single polymorphism. Thus far, only one group attempted to survey the entire genome, yet the results have not been replicated, are inconclusive and difficult to interpret, as long as an underpowered cohort was studied with inadequate coverage of ~80,000 SNPs [Obara et al, 2003; Ohtsubo et al, 2005]. Moreover, 77% of all published candidate-gene studies reported positive findings, an observation that is likely explained by a combination of high rate of false positives and a strong publication bias, whereas the statistical effect of the study of the same patient cohorts for multiple polymorphisms has never been accounted for in the literature [Kirylyuk et al, 2010]. Most findings were not reproduced in other populations. None of the above problems is unique to the field of IgAN and for these reasons, new general guidelines aimed at improving the design and execution of genetic association studies have recently been formulated [von Elm et al, 2007; Little et al, 2009].

In the post-genomic era, there has been a renewed interest in conducting genetic association studies, especially SNP-based, whole-genome association studies, to identify genetic variations associated with the development and/or progression of a number of common human diseases. This renewed interest reflects the important finding that linkage disequilibrium (LD), the phenomenon that particular alleles at nearby sites can co-occur on the same haplotype more often than expected by chance [Goldstein, 2001; Wahl et al, 2003] is highly structured into discrete blocks separated by hotspots for recombination. The haplotype block model for LD has important implications for the way in which genetic association studies should now be conducted, and may explain at least in part the problem of repeated non-replication of results that has plagued such studies in the past. Based on the haplotype block model of LD, the ACE I/D polymorphism is a single marker variant in the ACE gene, whereas it is unknown yet whether the D allele defines a simple population of subjects at risk for disease or not. The lumping of subgroups defined by haplotypes that share the D allele may explain at least in part the basis for discrepant reports of genetic association with disease.

Nowadays the common SNP haplotype block model is considered essential for the credibility of a study [Couser, 2003] and genetic association studies, especially family based, that employ one or more methodologically valid approaches and satisfy the minimum rigorous conditions for a reliable genetic association study are viewed as studies with solid documentation. These include mainly studies employing biologic plausibility, haplotype relative risk analysis to identify statistically significant “at-risk haplotype[s]” associated with small *P* values, use of family-based methodologies, such as the transmission equilibrium test (TDT/sib-TDT) or the family-based association test (FBAT) to directly study trios/sib-trios and extended families or to verify the absence of significant population stratification bias (admixture) inherent in population-based case-control association studies, and the study of moderately large i.e., adequately powered] cohorts. To date, very few studies examining candidate genes have employed the family-based TDT study methodology and/or analysis of “at-risk” haplotypes, reflecting the emergence of the first studies to attempt to satisfy minimum criteria for a valid association study.

A family- and haplotype-based association study employing the TDT methodology has shown that 2093C and 2180T SNP variants in the 3'-untranslated region of the *Megsin* gene

were significantly more frequently transmitted from heterozygous parents to patients than expected in the extended TDT analysis (increased co-transmission in 232 Chinese families,  $P < 0.001$ ). In addition, haplotype relative risk (HRR) analyses showed that these same SNP alleles were more often transmitted to patients (HRR = 1.568,  $P < 0.014$  for the 2093C allele; HRR = 2.114,  $P < 0.001$  for the 2180T allele) [Li YJ et al, 2004]. The same group using a similar approach recently reported that the *Megsin* 23167G SNP variant is associated with both susceptibility and progression of IgAN in 435 Chinese patients and their family members using TDT and HRR analyses [Takei et al, 2006]. The GG genotype was found to be associated with severe histologic lesions and disease progression. Megsin is a member of the serpin (serine proteinase inhibitor) superfamily that is upregulated in the context of mesangial proliferation and extracellular matrix expansion in IgAN, and therefore represents a strong candidate gene for susceptibility to IgAN. Lately, the gene encoding Cosmc, a C1Gal-T1 chaperone protein which also mediates IgA O-galactosylation was studied as a candidate gene involved in the pathogenesis of IgAN but no evidence for a role for Cosmc mutations was reported [Malycha et al, 2009].

### 2.3 IgAN consortium

The IgAN Biobank, coordinated by F.P. Schena, contains at minimum 72 multiplex extended pedigrees, 159 trios, and 1,068 cases and 1,040 matched controls. All subjects enrolled are white and belong to various geographic areas from Germany, Italy, and Greece [Schena et al, 2005]. Aiming at a genome wide linkage study, which has been considered the most promising approach to identify IgAN susceptibility genes, a group of investigators constituted the European IgAN Consortium which was initially funded by the European Union. DNA samples of IgAN patients and relatives belonging to 74 multiple extended pedigrees were collected. Moreover, 166 trios (affected sons or daughters and their healthy parents), 1,085 patients with biopsy-proven IgAN and 1,125 healthy subjects were included in the Biobank. In combination with linkage analysis, family based candidate gene association studies were also applied in an effort to discover responsible genes and overcome obstacles inherent the genetic analysis of complex traits such as IgAN.

*Linkage Analysis Studies* – The European IgAN Consortium performed the first genome-wide scan involving 22 Italian multiplex IgAN families [Bisceglia L et al, 2006]. A total of 186 individuals (59 affected and 127 unaffected) were genotyped and included in a two-stage linkage analysis. The regions 4q26–31 and 17q12–22 exhibited the strongest evidence of linkage by non-parametric analysis (best p values of 0.0025 and 0.0045, respectively). These localizations were also supported by multipoint parametric analysis where a peak LOD score of 1.83 ( $\alpha=0.50$ ) and of 2.56 ( $\alpha=0.65$ ), respectively, were obtained using the affected only dominant model, and by allowing for the presence of genetic heterogeneity. These regions became the second (IGAN2) and third (IGAN3) genetic locus candidates to contain causative and/or susceptibility genes for familial IgAN. Other regions did not reach the threshold of a suggestive or significant LOD score; however, the enrolment of additional IgAN families means that these chromosomal regions may be explored in the near future. The above results provide further evidence for genetic heterogeneity among IgAN families. Evidence of linkage to multiple chromosomal regions is consistent with both an oligo/polygenic and a multiple susceptibility gene model for familial IgAN with



small/moderate effects in determining the pathological phenotype. The analysis of the known genes located in these two novel loci (positional information procedure), carried out consulting the National Center for Biotechnology Information, identified some potential candidate genes such as the transient receptor potential channel 3 (TRPC3) gene, the interleukin-2 (IL-2) gene, and the IL-21 gene located in 4q26-31, which could be largely involved in the unbalanced Th1/Th2 immune response reported in IgAN patients. In addition, the histone deacetylase 5 (HD5) gene and the granulin (GRN) gene located on the 17q12-22 region, which could be involved in the immune-response deregulation, will also be considered. Family-based association studies, evaluating the distribution of these candidate gene polymorphisms, are in progress.

*Microarray Studies* – Different high-throughput gene analysis techniques can be used for obtaining transcriptome profiling of renal diseases. Microarray analysis represents the best and the latest approach to gain information on global gene expression. Genome-wide linkage analyses have identified at least three locus candidates containing IgAN susceptibility genes, although no specific gene(s) have been discovered. Microarrays are now in use to fingerprint the pathological process.

A published study postulated that changes in gene expression patterns in circulating leukocytes of IgAN patients may correlate with renal disease activity [Preston et al, 2004]. The investigators identified 14 upregulated genes. The BTG2, NCUBE1, FLJ2948, SRPK1, LYZ, GIG2 and IL-8 genes correlated with serum creatinine levels and the PMAIP1, SRPK1, SSI-3, LYZ and PTGS2 genes correlated with higher values of creatinine clearance, thus implying that the latter group of genes may provide a protective effect, while the overexpression of other genes such as B3GNT5, AXUD1 and GIG-2 indicated a worse prognosis. This gene signature reflected kidney function and did not correlate with hematuria or proteinuria. The authors concluded that studies carried out on large populations of IgAN patients will be necessary to confirm that the leukocyte gene expression profile can be used as a marker for diagnosis and for predicting outcome. The European IgAN Consortium has recently organized a protocol for studying gene expression in peripheral blood mononuclear cells (PBMC) and their subpopulations from IgAN patients with different clinical and histological patterns. Cox et al [2010] conducted a whole-genome expression study to identify genes and pathways differently modulated in peripheral blood leukocytes of IgAN patients. Gene expression of leukocytes demonstrated the hyperactivity of two important pathways as the canonical WNT- $\beta$  catenin and the PI3k/Akt pathways. The abnormal WNT signalling was also confirmed in IgAN patient's monocytes and to a less extent in B lymphocytes. Low gene expression of inversion and phosphatase and tensin homolog (PTEN) are responsible for the hyperactivation of these two pathways that enhance cell proliferation through lymphoid enhancer factor-1 (LEF-1) of which the gene is located within our previously described region 4q26-31 linked to IgAN [Bisceglia et al, 2006]. Finally, the hyperactivation of the PI3k/Akt pathway is in linkage with the upregulation of the immunoproteasome in peripheral blood mononuclear cells of IgAN patients, reported by Coppo et al, [2009].

Expression profiling using serial analysis of gene expression (SAGE) and microarray techniques allows global description of expressed genes present in renal tissue. This is a high throughput genomics technology which enables the simultaneous determination of a large number of genes from tissue samples. Preston et al identified 13 upregulated genes in IgAN renal biopsy samples. The cluster analysis identified 3 clusters with 7, 12 and 1

involved gene, respectively [Preston et al, 2004]. The expression levels of these genes were then examined on expanded RNA samples from other renal biopsies, leukocyte samples and cultured primary cells. Data demonstrated the involvement of the genes GABP and STAT3 in cluster I, and gp330 (megalin), MBP45K, MEF2, Oct1 and GABX in cluster II. The use of laser-capture microdissection applied to renal biopsy samples in combination with differential gene expression analysis is expected to provide novel knowledge in the search for IgAN candidate genes.

*Candidate genes association studies* - The IgAN Consortium takes care of the collection of biological samples from large homogeneous cohorts of IgAN patients, their parents and their first degree relatives, and family-based association studies are preferred to analyze the role of some candidate genes. A family-based association study, including 53 patients, 45 complete trios, 4 incomplete trios and 36 discordant siblings, evaluated the impact of some Th1/Th2/Th3/TR-type lymphocyte and monocyte/macrophage cytokines on IgAN susceptibility [Schena FP et al, 2006]. Cytokine gene polymorphisms with a potential regulatory role on their production were investigated using the family-based association test (FBAT): IFN $\gamma$  intron-1 CA-repeat at position 1349-1373; IL-13 -1055C/T; TGF $\beta$  915G/C; IL-10 5'-proximal and distal microsatellites; TNF $\alpha$  -308G/A, -238G/A. The FBAT multi-allelic analysis showed an association between IFN $\gamma$  polymorphism and susceptibility to IgAN ( $p=0.03$ ). The bi-allelic analysis showed that the 13-CA repeat allele was preferentially transmitted to the affected individuals ( $p=0.006$ ; Bonferroni  $p=0.04$ ). The direct sequencing of IFN $\gamma$  amplicons showed a strict association between the 13-CA repeat allele and the A variant of the +874T/A SNP (rs2430561) directly adjacent to the 5' end of the microsatellite. The in vitro production of IFN $\gamma$  evaluated in PBMC from 10 genotyped patients demonstrated a correlation between the +874A allele and a lower production of IFN $\gamma$  ( $p=0.028$ ). Notably, the +874A variant was associated with transcriptional downregulation of IFN $\gamma$  gene promoter activity, consistent with the known role of NF- $\kappa$ B in the transcriptional regulation of the IFN $\gamma$  gene.

The occurrence of the +874A variant is responsible for the low production of IFN $\gamma$  and predisposes to a preferential Th2-mediated immune response. The predominance of this variant in individuals with IgAN may be responsible for the onset of the disease. This unbalanced Th2 cytokine production in response to upper respiratory tract infections may be a significant pathogenic factor in human IgAN. The prevalence of Th2 cytokines may also explain the abnormality in IgA1 glycosylation occurring in IgAN patients and the concomitant formation of circulating IgA1-IgG immune complexes. Hyperfunction of Th2 cells and cytokine polarity are linked to a more nephritogenic pattern of IgA1 glycosylation in the animal model, and the decreased glycosylation of IgA1 elicited by Th2 cytokines is blunted in vitro by the addition of IFN $\gamma$  [Ebihara et al, 2008]. The core 1  $\beta$ 1,3-galactosyltransferase (C1Gal-T1) is suspected to be involved in the abnormal glycosylation process of IgA1 in IgAN. With the genetic characterization of the enzymes responsible for O-glycosylation of IgA1, it has been possible to study changes in the O-glycosylation of IgA1 at a genetic level. Most recently two groups [Pirulli et al, 2009; Li GS et al, 2007] have independently found that SNPs in the C1Gal-T1 gene are associated with a genetic susceptibility to IgAN in Chinese and Italian populations, albeit it is not clear how these polymorphisms relate to changes in the functional activity of C1Gal-T1. The C1Gal-T1 gene complete sequence analysis was performed in 284 IgAN patients and 234 healthy controls. A statistically significant association of the genotype 1365G/G with

susceptibility to IgAN ( $\chi^2=17.58$ ,  $p<0.0001$ , odds ratio 2.57 [95% CI: 1.64–4.04]), but not with the progression of the disease, was found [Pirulli et al, 2009]. The latter case-control association study demonstrates that the low expression of C1Gal-T1 seems to confer susceptibility to IgAN.

In conclusion, to date the Consortium has identified two loci (located on chromosomes 4q26–31 and 17q12–22), in addition to a previous study which described the first IgAN locus on chromosome 6q22–23. The functional mapping of genes involved in the disease proceeds from the identification of susceptibility loci identified by linkage analysis (step 1) to the isolation of candidate genes within gene disease-susceptibility loci, after obtaining information by microarray analysis carried out on peripheral leukocytes and renal tissue samples (step 2). Next steps will be the design of RNA interference agents against selected genes (step 3) and the application of systematically tested effect of RNA agents on functional cellular assay (step 4). The above combined high-throughput technologies will give information on the pathogenic mechanisms of IgAN. In addition, these data may indicate potential targets for screening, prevention and early diagnosis of the disease and more appropriate and effective treatment.

### 3. Treatment of IgAN

Treatment strategy for IgAN remains a controversial issue, even more as published randomized controlled trials (RCTs) on this topic are few and most studies are underpowered to provide definitive information. Furthermore, the disease heterogeneity, its clinical course along with the slow rate of GFR decline (1 to 3 mL/min per year) seen in many patients hinders the ability to perform adequate studies. An additional obstacle is the fact that a significant percentage of the patients have only minimal clinical presentation, such as isolated microhematuria, no or minimal proteinuria and normal GFR, and are often not biopsied or even identified. Still no treatment is known to modify mesangial deposition of IgA, which obviously reflects our incomplete knowledge of immunopathogenesis of IgAN [Barratt et al, 2007], and available treatment options are directed mostly at downstream immune and inflammatory events that may lead on to renal scarring. Therefore, as more pathogenetic details, the genetic substrate and heterogeneity of IgAN become increasingly understood, novel treatment strategies with solid therapeutic targets are anticipated, as long as the traditional therapies used until today seem symptomatic rather than etiologic. The discovery and establishment of novel biomarkers associated with the disease activity and outcome will provide the prognostic and therapeutic tool for more accurate and clear therapeutic targeting.

However, there seems to be a consensus regarding patient selection for the different therapeutic approaches. Patient selection for therapy is based in part upon the perceived risk of progressive kidney disease:

- Patients with isolated hematuria, no or minimal proteinuria (<500mg/day), a normal GFR and no signs of progressive disease, such as increasing proteinuria, blood pressure, and/or serum creatinine, are typically not treated.
- Patients with persistent proteinuria (>500 mg/day), normal or only slightly reduced GFR (>50mL/min) that is not declining rapidly, and only mild to moderate histologic findings on renal biopsy are managed with general interventions to slow progression with ACE-inhibitors or angiotensin receptor blockers (ARB) or with combination therapy of corticosteroid (6 months) and ACE-inhibitors forever.

- Patients with more severe or rapidly progressive disease (eg, proteinuria > 1g or proteinuria persisting despite ACE inhibitor/ARB therapy, rising serum creatinine, and/or renal biopsy with more severe histologic findings, but no significant chronic changes) may benefit from immunosuppressive therapy in addition to non-immunosuppressive interventions to slow disease progression.
- In the future, the Oxford histologic classification system, once validated, is anticipated to become a useful prognostic tool that could lead in the future our therapeutic choices [Working Group of the International IgAN Network and the Renal Pathology Society, 2010].

### 3.1 Monitoring disease activity

Up to date, there are no specific markers to identify continued immunologic activity. Instead, the clinical parameters typically used as the main therapeutic criterion are the urine sediment, protein excretion and the serum creatinine concentration. Persistent hematuria is generally a marker of persistent immunologic activity, but not necessarily of progressive disease. This finding may be a sign of a "smoldering" segmental necrotizing lesion, suggestive of "capillaritis." Hematuria alone does not require any form of therapy. Proteinuria, rather than hematuria alone, is a marker of more severe disease [Donadio et al, 2002]. Increasing proteinuria may be due to one of two factors: ongoing active disease; and secondary glomerular injury due to non-immunologic progression. It is often not possible to distinguish between these two possibilities, except for a rapid increase in protein excretion which is only seen with active disease. Protein excretion most often falls with ACE inhibitor/ARB therapy and the degree of proteinuria is, as described below, one of the end points of such therapy. Protein excretion also may fall spontaneously, particularly during recovery from an acute episode and perhaps in children, and following effective immunosuppressive therapy. Finally, serum creatinine, unless it is rapidly rising, permits an estimation of the GFR. As noted above, most patients with chronic IgAN have stable or slowly progressive disease. The rate of GFR decline is often as low as 1 to 3 mL/min per year, a change that will not detectably raise the serum creatinine above normal levels for many years [Rekola et al, 1991]. Thus, a stable and even normal serum creatinine does not necessarily indicate stable disease.

The establishment of accurate biomarkers is necessary for the optimal categorization and treatment of patients with IgAN. Over the last few years specific urine biomolecules have been proposed as probable biomarkers to be used in the prognosis and therapeutic strategy in patients with IgAN. Two recent studies identified urine epidermal growth factor and monocyte chemoattractant protein-1 as strong independent predictors of renal outcome in patients with IgAN [Torres et al, 2008; Stangou et al, 2009]. These and other biomolecules are being validated as probable biomarkers of IgAN in studies underway.

### 3.2 Non-immunosuppressive therapies

Three main non-immunosuppressive therapies are in use in IgAN [Barratt & Feehally, 2006; Appel & Waldman, 2006]:

- ACE inhibitors or ARB, to control blood pressure and to slow down progression of the renal disease.
- Statin therapy, for lipid-lowering in selected patients, to lower cardiovascular risk and possibly reduce disease progression.
- Fish oil (omega-3 fatty acids) may also be beneficial in certain cases.



### 3.2.1 Angiotensin inhibition

The progression of IgAN may be slowed by anti-hypertensive and anti-proteinuric therapy that can minimize secondary glomerular injury [Kanno et al, 2000]. The treatment goals with angiotensin inhibition are the same as those in other forms of proteinuric chronic kidney disease as described in the K/DOQI guidelines [K/DOQI, 2004]. ACE inhibitors and ARBs act by reducing the intraglomerular pressure and by directly improving the size-selective properties of the glomerular capillary wall, both of which contribute to reducing protein excretion [Remuzzi et al, 1991; Maschio et al, 1994].

Both observational studies [Cattran et al, 1994; Kanno et al, 2005] and small randomized trials [Maschio et al, 1994; Praga et al, 2003; Li PK et al, 2006] have provided suggestive evidence that ACE inhibitors or ARBs are more effective than other antihypertensive drugs in slowing the progressive decline in GFR in IgAN as they are in other forms of chronic proteinuric kidney disease. Praga et al in their randomized trial in 44 IgAN patients with proteinuria ( $\geq 0.5$  g/day, mean 1.9 g/day) and a serum creatinine concentration  $\leq 1.5$  mg/dL at baseline, found a significant decrease in proteinuria in the enalapril group (1.9 g/day at baseline to 0.9 g/day at the last visit) and a significantly higher renal survival, defined as less than a 50 percent increase in the serum creatinine concentration, at 6 years of follow up [Praga et al, 2003]. More recently, Li et al in their double-blind randomized placebo-controlled HKVIN trial in 109 Chinese patients with protein excretion  $\geq 1$  g/day (mean  $\sim 2.0$  g/day), found a better renal survival, defined as doubling of serum creatinine or ESRD, a significant improvement in proteinuria (33 % reduction in proteinuria) and a slower rate of decline in GFR (4.6 versus 6.9 mL/min per year) in the valsartan group compared to placebo [Li PK et al, 2006]. Similarly, the IgACE trial in 65 young patients with moderate proteinuria (between 1 and 3.5 grams/day per  $1.73 \text{ m}^2$ ) and creatinine clearance  $>50$  mL/min per  $1.73 \text{ m}^2$  revealed a better renal survival (fewer patients with  $>30\%$  decline in renal function) and significant improvement in proteinuria at 38 months of follow-up in the benazepril group compared to the placebo group [Coppo, 2007].

Normotensive patients who excrete less than 500 mg of protein per day are not typically treated with angiotensin inhibition. However, because most patients progress slowly over time, monitoring of the serum creatinine and protein excretion at yearly intervals is recommended. Angiotensin inhibition should be started if there is evidence of progressive disease and protein excretion above 500 mg/day.

The addition of an ARB to an ACE inhibitor in patients with IgAN seems to exert a further antiproteinuric effect [Russo et al, 1999, 2001], albeit there are no randomized trials showing that this regimen improves renal outcomes. This finding is consistent with meta-analyses of trials in different glomerular diseases, the largest of which found a significant 18 to 25% greater reduction in proteinuria with combined ACE inhibitors and ARBs compared to monotherapy [Kunz et al, 2008; Catapano et al, 2008]. The rationale for this combination therapy is the assumption that ARBs would counteract the AT1-mediated effect of residual angiotensin II formation by non-ACE enzymes like chymase, whereas ACE inhibitors would additionally increase the level of kinins. Furthermore, ACE inhibitors as well as ARBs would synergistically elevate the levels of angiotensin, which also might promote vasodilation. Finally, combining both drug classes might simply provide a higher degree of blockade of the classic renin-angiotensin system pathways [Alexopoulos, 2004]. However, any anticipated benefits from this combination should be weighted against possible adverse effects in individual patients; this is important especially given the findings from the ONTARGET trial in 25,620 patients with vascular

disease or diabetes, where an increase in adverse side effects (including a possible increase in mortality) in patients who received combination therapy with an ACE inhibitor and ARB was shown, compared to those who received monotherapy [ONTARGET Investigators, 2008; Mann et al, 2008].

### 3.2.2 Lipid-lowering therapy

Chronic kidney disease is associated with a marked increase in cardiovascular risk, and is now considered a coronary artery disease risk equivalent. Furthermore, lipid-lowering with statins has been associated with a slower rate of loss of GFR in patients in some patients with mild to moderate CKD, and there are indications for such a beneficial effect of statins in patients with IgAN as well [Kano et al, 2003]. Therefore, it seems rational that all patients with decreased kidney function and/or hypercholesterolemia should receive lipid-lowering therapy with a statin, with treatment goals similar to that in patients with underlying coronary heart disease.

### 3.2.3 Fish oil

The rationale for using fish oil (omega-3 fatty acids) in IgAN is based on the premise that they may limit the production or action of cytokines and eicosanoids evoked by the initial or by repeated immunologic renal injury, and the resulting production of mediators involved in renal damage [Donadio, 1991]. Randomized controlled trials evaluating fish oil in patients with IgAN have reported conflicting results [Donadio et al, 1994; Alexopoulos et al, 2004; Donadio et al, 1999, 2001; Bennett et al, 1989; Pettersson et al, 1994; Hogg et al, 2006; Ferraro et al, 2009]. In the largest and most well documented and conducted randomized trial in 106 patients with baseline creatinine clearance 80 mL/min and protein excretion of 2.5 to 3 g/day, Donadio et al found better patient and renal outcomes at 4 years, extended also at >6 years, in patients having received 12g of fish oil for 2 years, compared to patients having received a similar amount of olive oil [Donadio et al, 1994, 1999]. Similarly, in a controlled study of 14 IgAN patients and 14 controls, a low dose of fish oil (0.85 g eicosapentaenoic acid and 0.57 g phytohemagglutinin) was found effective in slowing renal progression in high-risk patients with IgAN and particularly those with advanced renal disease [Alexopoulos et al, 2004]. On the other hand, in the randomized controlled trial by the Southwest Pediatric Nephrology Study Group in 96 patients with IgAN, mean GFR >100 mL/min per 1.73 m<sup>2</sup> and proteinuria 1.4 to 2.2 g/day, no significant benefit in the renal outcome was found in patients assigned to omega-3 fatty acids (4 g/day) for two years compared to the patients assigned to either alternate day prednisone or placebo [Hogg et al, 2006]. On the basis of the existing data, fish oil can be tried in addition to ACE inhibitors or ARBs in patients with protein excretion >500 to 1000 mg/day, a gradual reduction in GFR, and mild to moderate histologic lesions [Alexopoulos E, 2004].

### 3.3 Immunosuppressive therapy

The optimal role of immunosuppressive therapy in IgAN is uncertain [Barratt & Feehally, 2006; Appel & Waldman, 2006]. A variety of regimens have been used, mostly consisting of corticosteroids alone or with other immunosuppressive drugs. The available studies are not conclusive since most are relatively small and have limited follow-up, and the results are sometimes conflicting [D'Amico, 1992; Alamartine et al, 1991; Alexopoulos, 2004; Strippoli et al, 2003; Laville & Alamartine, 2004; Ballardie, 2004; Julian, 2000; Dillon, 2001]. There is

rather consensus that mild, stable, or very slowly progressive IgAN should not be treated with corticosteroids or other immunosuppressive therapies, given the limited evidence of benefit and their known toxicity from chronic use [Floege & Eitner, 2005; Locatelli et al, 1999]. Corticosteroid or other immunosuppressive therapy should only be attempted in patients with clinical and histologic evidence of active inflammation (eg, hematuria and/or proliferative or necrotizing glomerular changes). Patients with chronic kidney disease with significant tubulointerstitial fibrosis and glomerulosclerosis are not likely to benefit from such therapy and are likely to be harmed from the side effects.

### 3.3.1 Corticosteroids

Current evidence regarding the potential benefit of corticosteroid therapy in IgAN are rather limited, as long as most of the studies performed are uncontrolled retrospective observations; moreover, the few available randomized controlled trials are rather small and in most of them the standard recommendations for proteinuria and blood pressure goals were not followed, limiting thus the applicability of the findings to current practice. Whatsoever, these studies point towards a beneficial effect of corticosteroid therapy (administered for 6 up to >24 months) in proteinuria and perhaps in renal survival [Floege & Eitner, 2005; Nolin & Courteau, 1999; Kobayashi Y et al, 1989, 1996; Pozzi et al, 1999, 2004; Tamoura et al, 2001; Katafuchi et al, 2003; Hotta et al, 2001; Moriyama et al, 2004; Lv et al, 2009, Manno et al, 2009], probably preferentially in individuals with preserved kidney function (eg, creatinine clearance above 50 mL/min) [Kobayashi et al, 1989, 1996; Pozzi et al, 1999, 2004]. Two randomised clinical trials demonstrated the benefit of the combination therapy with corticosteroids and ACE inhibitors on long-term follow-up in proteinuric IgAN patients. Lv et al (2009) evaluated the efficacy of the combination therapy versus ACE-inhibitors alone in a small number of IgAN patients with mild or moderate histologic lesions and with a follow-up period that was too short to evaluate the renal survival. Data demonstrated that the combination therapy reduced better the urinary protein excretion than the administration of ACE-inhibitors alone.

Even more, Manno et al enrolled 97 IgAN patients with moderate histologic lesion (see IgAN classification of F.P. Schena in Manno et al., 2007) daily proteinuria more than 1.0g and estimated GFR more than 50 ml/min/1.73m<sup>2</sup>. Patients were randomly allocated to receive a 6-month course of oral prednisone plus ramipril or ramipril alone for the total duration of the follow-up (96 months). The combination of corticosteroids and ramipril provided less probability of renal disease progression because induced the decline of GFR and daily proteinuria. In an interesting recent meta-analysis of randomized and quasi-randomized controlled trials of corticosteroid treatment in IgAN against treatment without steroids, Zhou et al found that steroid therapy, especially long-term, is associated with a significant benefit in proteinuria and renal survival [Zhou et al, 2011].

In addition, the IgAN patients seemingly to benefit from prednisone therapy are those with nephrotic syndrome, little or no hematuria, preserved kidney function, minimal glomerular changes on light microscopy, and diffuse fusion of glomerular epithelial cell foot processes on electron microscopy. These histologic findings are characteristic of minimal change disease, and these patients behave accordingly, frequently developing a remission with corticosteroids and occasionally requiring cytotoxics for frequently relapsing proteinuria [Mustonen et al, 1983; Lai KN et al, 1986; Cheng et al, 1989]. Mesangial IgA deposits in these patients often disappear or are greatly reduced following steroid-induced remission [Cheng

et al, 1989]. Nephrotic syndrome can also occur with severe chronic IgAN and relatively advanced disease on renal biopsy. These patients do not seem to benefit from corticosteroid therapy alone [Mustonen et al, 1983; Lai KN et al, 1986].

### 3.3.2 Combined immunosuppressive therapy

Combined immunosuppressive therapy should only be attempted in patients with more severe active disease as defined by a more rapidly progressive clinical course and/or histologic evidence of severe active inflammation (eg, crescent formation). Early therapy is important because improvement is rare when the baseline serum creatinine concentration is greater than 3.0 mg/dL in the absence of crescentic glomerulonephritis [Alexopoulos E, 2004].

*Corticosteroids plus azathioprine* – Whether the addition of azathioprine provide any benefit to that of corticosteroids is still debatable. In a multicenter randomized trial by Pozzi et al in 207 patients with plasma creatinine  $\leq 2.0$  mg/dL and protein excretion  $>1.0$  g/day, at a median follow-up of 4.9 years, there was no difference neither in renal survival time, defined as the time to 50% increase in plasma creatinine from baseline, nor in the decrease in proteinuria between patients who received corticosteroids alone or along with azathioprine (1.5 mg/kg /day for six months) [Pozzi et al, 2010]. However, in the above study, only a rather small percentage of patients were receiving either ACE inhibitors or ARBs, and even fewer patients were receiving statins. Most recently, Stangou et al published a randomized, yet underpowered study in 22 patients with IgAN and eGFR $\geq 30$  mL/min, urine protein  $\geq 1$  g/day, blood pressure  $<130/80$  mmHg, who failed to respond to previous treatment with renin-angiotensin system inhibitors and poly-unsaturated fatty acids administered for at least 6 months. During the 5<sup>th</sup> year after the diagnosis was made, the patients were randomized to receive either methylprednisolone alone, or methyl-prednisolone in combination with azathioprine, for 12 months, while treatment with renin-angiotensin system inhibitors and poly-unsaturated fatty acids continued unchanged in both groups. Both, steroid treatment alone, or steroids in combination with azathioprine were found to be equally effective in reducing the severity of proteinuria and stabilizing renal function [Stangou et al, 2011].

*Corticosteroids plus cyclophosphamide* – There are evidence suggesting that patients with severe or progressive disease (eg, rising creatinine, nephrotic range proteinuria, and/or marked proliferation without crescents) who do not have significant chronic damage on kidney biopsy may benefit from combined immunosuppressive therapy with prednisone and cyclophosphamide. This regimen was evaluated in a study of Ballardie et al in 38 patients with IgAN and initially impaired renal function (baseline serum creatinine between 1.5 and 2.8 mg/dL, mean baseline protein excretion 4.0 to 4.5 g/day, no crescents on biopsy) that was declining at a relatively moderate rate (by at least 15% per year). Compared with the control group, the patients treated with combination therapy (prednisolone 40mg/day tapered to 10mg/day by two years plus low-dose cyclophosphamide for 3 months followed by low-dose azathioprine for at least 2 years) had a significant reduction in protein excretion during the first six months of therapy that persisted during follow-up (eg, reached 1.8 g/day in treatment group versus unchanged at 4.4 g/day in controls at one year). Renal survival was significantly higher in the treatment group at two (82 versus 68 percent) and five years (72 versus 6 percent). [Ballardie et al, 2002].



Uncontrolled reports in patients with crescentic, rapidly progressive glomerulonephritis suggest possible benefit from regimens similar to those used in idiopathic crescentic glomerulonephritis: intravenous pulse methylprednisolone followed by oral prednisone, intravenous or oral cyclophosphamide, and/or plasmapheresis [Welch et al, 1988; Lai KN et al, 1987a; Rocatello et al, 1995; McIntyre et al, 2001; Tumlin et al, 2003]. Corticosteroids may act in this setting by diminishing acute inflammatory injury rather than by correcting the abnormality in IgA production [Galla, 1995]. In a study by Rocatello et al, although a substantial clinical improvement was found with the administration of aggressive combination therapy (including pulse methylprednisolone, oral cyclophosphamide, and plasmapheresis) for 2 months in six patients with crescentic glomerulonephritis due to IgAN [Rocatello et al, 1995], yet cellular crescents failed to remit in repeat renal biopsy, whereas the disease continued to progress in half of the patients after therapy was discontinued. Limited data for a more prolonged course of aggressive immunosuppressive therapy (pulse methylprednisolone 15mg/kg/day for 3 days, followed by oral prednisolone 1 mg/kg/day for 60 days gradually tapered, along with monthly iv cyclophosphamide (0.5 g/m<sup>2</sup>) for 6 months) point towards a significant improvement in the serum creatinine and in protein excretion along with a significant reversion of cellular crescents and endocapillary proliferation [Tumlin et al, 2003].

These limited data suggest that patients with active crescentic glomerulonephritis who do not have significant chronic damage on kidney biopsy may benefit from therapy that initially includes intravenous cyclophosphamide. This is consistent with the benefit noted with a similar regimen in other forms of crescentic glomerulonephritis.

### 3.3.3 Other immunosuppressive agents

*Cyclosporine* – Cyclosporine has been investigated in small studies, and resulted in reduced proteinuria. In a recent study, Shin et al reported a significant benefit of cyclosporine therapy in proteinuria reduction and renal pathology regression in 14 children with IgAN and near normal creatinine clearance [Shin et al, 2010]. However, there are important issues of concern regarding its use in IgAN treatment, with most important the associated nephrotoxicity, which can lead to harmful effects on renal function [Lai KN et al, 1987b; Cattran, 1991], as well as the rapid disease relapse after drug discontinuation.

*Mycophenolate mofetil* – Small, prospective placebo-controlled randomized trials of mycophenolate mofetil (MMF) in which the patients were also treated with ACE inhibitors, have produced conflicting results, ranging from no benefit [Maes et al, 2004; Frisch et al, 2005] to a reduction in proteinuria and decrease in rate of decline of GFR [Tang et al, 2010]. A short course (< 6 months) of MMF in patients with persistent proteinuria (>1.5 g/day) and well-maintained renal function (serum creatinine <1.5 mg/dL) in addition to ACE inhibitor/ARB therapy may be considered in patients with well-preserved renal histology on biopsy. Current evidence does not support the use of MMF in patients with advanced disease (serum creatinine >2.5 to 3 mg/dL) [Cattran & Appel, 2011].

### 3.4 Other possible interventions

*Tonsillectomy* – Several retrospective studies have suggested that tonsillectomy, usually in combination with some immunosuppressive therapy, is associated with improved renal survival among patients with relatively mild renal injury [Hotta et al, 2001; Xie et al, 2003; Komatsu et al, 2008]. These non-randomized studies provide some evidence that

tonsillectomy may be effective in inducing remission of proteinuria and hematuria in patients with IgAN (ie, proteinuria >500 mg/day). However, there are no randomized trials of tonsillectomy in IgAN, the design of the above studies precludes any definitive conclusions regarding the overall efficacy of tonsillectomy in IgAN, while other studies reported negative results [Rasche et al, 1999].

*Low antigen diet* – The rationale for using a low antigen diet in IgAN, ie diet free of gluten, dairy products, eggs, and most meats, is that dietary macromolecules may be responsible for activating the mucosal IgA system. When given to 21 consecutive patients with IgAN, protein excretion fell markedly in all 12 patients whose baseline rate was more than 1g/day. In addition, repeat renal biopsy showed significant reductions in mesangial IgA and complement deposition and mesangial cellularity [Ferri et al, 1993]. However, the benefits in the above study have not been confirmed and a report using a gluten-free diet alone for several years was unable to document improvement in either proteinuria or renal function despite a reduction in the level of circulating IgA-containing immune complexes [Coppo et al, 1990].

*Intravenous immune globulin* – At least part of the rationale for intravenous immune globulin (IVIG) therapy in IgAN comes from the observation that a partial IgG deficiency, which could be corrected with IVIG, may predispose to infections that trigger flare-ups of the renal disease [Rostoker et al, 1989, 1994]. Despite the promising findings from two small studies with the administration of high-dose IVIG in severe IgAN, characterized by heavy proteinuria and a relatively rapid decline in GFR (reduction in protein excretion, prevention of GFR decline, decreased inflammatory activity and IgA deposition on repeat renal biopsy) [Rostoker et al, 1994; Rasche et al, 2006], these findings need to be confirmed by larger studies.

#### 4. Conclusion

Genetic susceptibility for IgAN exhibits a complex genetic pattern. To date various groups and the European IgAN Consortium have identified several loci. The extensive genetic studies under way with the use of delicate, high-throughput technologies will give information on the pathogenic mechanisms of IgAN. In addition, these data may indicate potential targets for screening, prevention and early diagnosis of the disease and more appropriate and effective treatment.

Summarizing the most updated data, following are concise treatment guidelines:

- Patients with isolated hematuria, no or minimal proteinuria (<0.5g/day), and a normal GFR need no treatment. Such patients should be periodically monitored at 6 to 12 month intervals to assess disease progression that might warrant therapy.
- Patients with persistent proteinuria (>0.5 or >1 g/day), should be treated with angiotensin inhibition (ACE inhibitor or ARB), with a target of a minimum reduction in protein excretion of at least 50 to 60% from baseline values and a goal protein excretion of <0.5 or <1 g/day.
- All patients who meet criteria for angiotensin inhibition may also be considered as candidates to receive fish oil.
- Patients with persistent nephrotic syndrome and/or chronic kidney disease who have dyslipidemia should be treated with a statin, primarily for cardiovascular protection.
- Corticosteroid therapy for at least 6 months is indicated in the following cases:

- a. In patients with acute onset of nephrotic syndrome and minimal changes beyond mesangial IgA deposits on renal biopsy (as in patients with minimal change disease).
- b. In patients with moderate renal lesions (eg, hematuria with persistent proteinuria >1 g/day and/or GFR>50ml/min) in association with ACE inhibitors or ARBs.
- For patients with severe disease at baseline (defined as initial serum creatinine >1.5 mg/dL) or progressive disease (eg, increasing serum creatinine and/or protein excretion) who do not have significant chronic damage on kidney biopsy, therapy with oral prednisone and cyclophosphamide is recommended.

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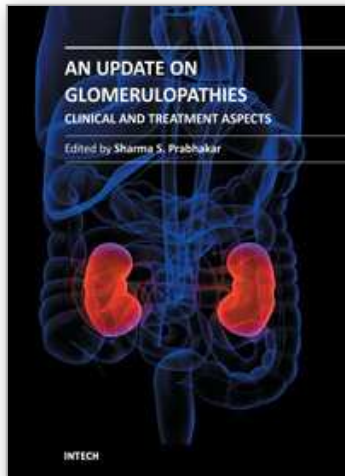
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## **An Update on Glomerulopathies - Clinical and Treatment Aspects**

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An Update on Glomerulopathies - Clinical and Treatment Aspects is a systemic overview of recent advances in clinical aspects and therapeutic options in major syndromes of glomerular pathology. The book contains twenty four chapters divided conveniently into five sections. The first section deals with primary glomerulopathies, and the second section is devoted to glomerulopathies complicating infectious conditions. The third section deals with systemic autoimmune disorders and vasculitides which constitute major causes of glomerular disease and often renal failure. The fourth section includes chapters discussing the glomerular involvement in some major metabolic and systemic conditions. The final section has chapters which relate to some general aspects of glomerular diseases. This book will form an excellent reference tool for practicing and academic nephrology community.

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